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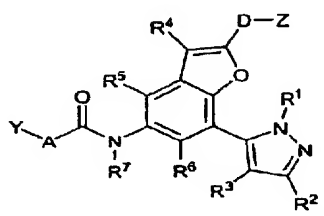

(I)

(57) Abstract: The present invention relates to benzofuran derivatives of the following formula (I) which are modulators of the serotonin 5-HT_{2A} receptor and are useful in the treatment of various diseases and disorders related to the 5-HT_{2A} receptor.

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BENZOFURAN DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} RECEPTOR

FIELD OF THE INVENTION

The present invention relates to benzofuran derivatives which are modulators of the serotonin 5-HT_{2A} receptor and are useful in the treatment of various diseases and disorders related to, for example, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy, and the like.

BACKGROUND OF THE INVENTION

G Protein coupled receptors

G Protein coupled receptors share a common structural motif of seven alpha helices (between 22 to 24 hydrophobic amino acids), each of which spans the cell membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified.

Under physiological conditions, G protein coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an

active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, e.g., lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT_1 through 5-HT_7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT_2 subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The human 5-HT_{2C} receptor was first isolated and cloned in 1987, and the human 5-HT_{2A} receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT_{2A} and 5-HT_{2C} receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{1C} receptor (now known as the 5-HT_{2C} receptor). U.S. Patent Numbers 5,661,024 and 6,541,209 describe the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{2A} receptor.

5-HT_{2A} Receptor

The 5-HT_{2A} receptor has been shown to be associated with a number of diseases and disorders, and its modulation is believed to have therapeutic potential.

5-HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and

thus be a potential treatment as an antiplatelet therapy (see Satimura, K, et al., Clin Cardiol 2002 Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost 1991 Sep 2;66(3):355-60).

5-HT_{2A} inverse agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications (see Br. Med. J. 298: 424 – 430, 1989), Arterial thrombosis (see, Pawlak, D. et al. Thrombosis Research 90: 259 – 270, 1998), atherosclerosis (see, Hayashi, T. et al. Atherosclerosis 168: 23 – 31, 2003), vasoconstriction, caused by serotonin (see, Fujiwara, T. and Chiba, S. Journal of Cardiovascular Pharmacology 26: 503 – 510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. et al. Am Heart J. 145:e16 2003). It can also be used alone or in combination with thrombolytic therapy, for example, tPA (see, Yamashita, T. et al. Haemostasis 30:321 – 332, 2000), to provide cardioprotection following MI or postischemic myocardial dysfunction (see, Muto, T. et al. Mol. Cell. Biochem. 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see, Horibe, E. Circulation Research 68: 68 – 72, 2004), and the like, including complications resulting therefrom.

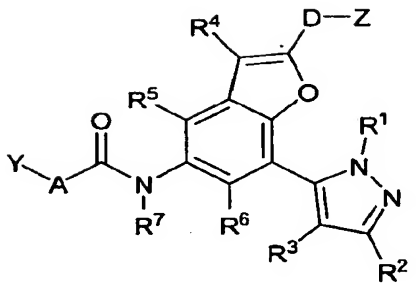
5-HT_{2A} inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and artherosclerosis (see Nomura, Shosaku, et al. Blood Coagulation and Fibrinolysis 2005, 16, 423-428).

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721). Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976).

Dysfunction of the 5-HT_{2A} receptor has also been linked with various sleep disorders, diabetic-related pathologies, glaucoma, progressive multifocal leukoencephalopathy (PML), hypertension, and pain. Accordingly, new compounds that act as 5-HT_{2A} receptor modulators are consistently needed to develop new drugs for the treatment of the above-mentioned and other diseases. The compounds, compositions, and methods described herein are directed toward this end.

SUMMARY OF THE INVENTION

The present invention provides, *inter alia*, compounds of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein constituent members are provided herein.

The present invention further provides compositions comprising at least one compound of Formula I, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention further provides methods of preparing pharmaceutical compositions of the invention by admixing at least one compound of Formula I, or pharmaceutically acceptable salt thereof, with at least one pharmaceutically acceptable carrier.

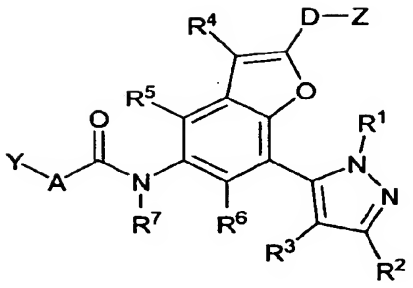
The present invention further provides methods of modulating the 5-HT_{2A} receptor by contacting the receptor with a compound of Formula I, or pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a 5-HT_{2A} receptor related disease or disorder in a patient by administering to the patient a therapeutically effective amount of a compound of Formula I, pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

The present invention further provides methods of treating diseases and disorders in a patient related to, for example, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy, and the like, by administering to the patient a therapeutically effective amount of a compound of Formula I, pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, compounds that modulate the 5-HT_{2A} receptor and have Formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

A is absent, O or NR^8;

D is absent, C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, O, S, NR^9, CO, COO, $CONR^9$, SO, SO_2, $SONR^9$, or NR^9CONR^{10};

Y is C_{1-10} alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$;

Z is H, C_{1-10} alkyl, NR'R", aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is H or C_{1-6} alkyl;

R^2 and R^3 are independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}C(O)OR^{a2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^4, R^5, and R^6 are independently selected from H, halo, and C_{1-4} alkyl;

R^7, R^8, R^9, and R^{10} are independently selected from H and C_{1-4} alkyl;

Cy is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$;

R' and R" are independently selected from H, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl,

arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a, R^{a1}, and R^{a2} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^b, R^{b1}, and R^{b2} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^c and R^d are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^{c1} and R^{d1} are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^{c2} and R^{d2} are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; and

R^e, R^{e1}, and R^{e2} are independently selected from H, CN, and NO_2.

In some embodiments, A is absent.

In some embodiments, A is O.

In some embodiments, A is NR^8.

In some embodiments, A is NH.

In some embodiments, Y is C_{1-10} alkyl, aryl, or heteroaryl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is C_{1-10} alkyl or aryl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is aryl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is phenyl optionally substituted by Cy.

In some embodiments, Y is phenyl optionally substituted by Cy, wherein said Cy is located at the *meta* or *para* position.

In some embodiments, Y is C_{1-10} alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^c)NR^cR^d$, $NR^cC(=NR^c)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is C_{1-10} alkyl.

In some embodiments, Y is isobutyl.

In some embodiments, Y is phenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^c)NR^cR^d$, $NR^cC(=NR^c)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, Y is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^a.

In some embodiments, D is absent, C_{1-4} alkylene, or COO.

In some embodiments, D is absent.

In some embodiments, D is C_{1-4} alkylene.

In some embodiments, D is COO.

In some embodiments, Z is H, C_{1-10} alkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, Z is H, C_{1-10} alkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, Z is H, C_{1-10} alkyl, or heterocycloalkyl.

In some embodiments, Z is H.

In some embodiments, Z is C_{1-10} alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$,

$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, Z is heterocycloalkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, Z is pyrrolidinyl, piperidinyl, piperazinyl, or morpholino, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, –D-Z is, H, C(O)O-(C_{1-10} alkyl), COOH, or heterocycloalkyl-(C_{1-10}) alkyl.

In some embodiments, R^1 is H or methyl.

In some embodiments, R^1 is methyl.

In some embodiments, R^2 and R^3 are independently selected from H and halo.

In some embodiments, R^2 is H.

In some embodiments, R^3 is H or halo.

In some embodiments, R^3 is H.

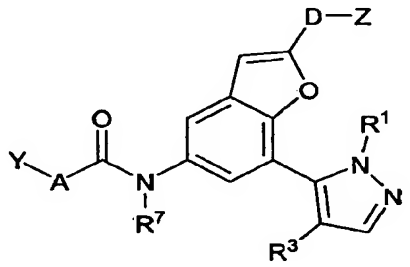
In some embodiments, R^3 is halo.

In some embodiments, R^3 is Br.

In some embodiments, R^4, R^5, and R^6 are each H.

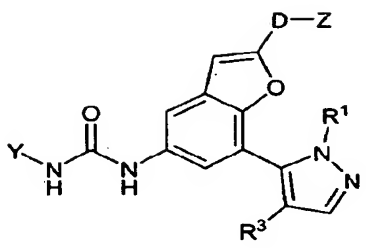
In some embodiments, R^7 is H.

In some embodiments, the compounds have Formula II:

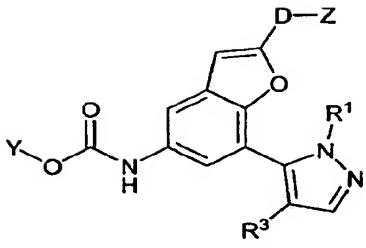


II.

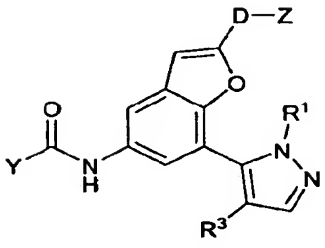
In some embodiments, the compounds have Formula IIIa, IIIb, or IIIc:



IIIa



IIIb



IIIc.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

It is further intended that the compounds of the invention are stable. As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, the term "alkylene" refers to a linking alkyl group.

As used herein, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Example alkenyl groups include ethenyl, propenyl, and the like.

As used herein, "alkenylene" refers to a linking alkenyl group.

As used herein, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include ethynyl, propynyl, and the like.

As used herein, "alkynylene" refers to a linking alkynyl group.

As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5, and the like.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "cycloalkyl" refers to non-aromatic carbocycles including cyclized alkyl, and alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems, including spirocycles. In some embodiments, cycloalkyl groups can have from 3 to about 20 carbon atoms, 3 to about 14 carbon atoms, 3 to about 10 carbon atoms, or 3 to 7 carbon atoms. Cycloalkyl groups can further have 0, 1, 2, or 3 double bonds. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of pentane, pentene, hexane, and the like. A cycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized, for example, having an oxo or sulfido substituent. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like.

As used herein, a "heteroaryl" group refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Any ring-forming N atom in a heteroaryl group can also be oxidized to form an N-oxo moiety. Examples of heteroaryl groups include without limitation, pyridyl, N-oxopyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to a non-aromatic heterocycle where one or more of the ring-forming atoms is a heteroatom such as an O, N, or S atom. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems as well as spirocycles. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like. Ring-forming carbon atoms and ring-

forming heteroatoms can also be substituted with one or two oxo or sulfide groups. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles such as indolene and isoindolene groups. A heterocycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 20, 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "alkoxy" refers to an –O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, "haloalkoxy" refers to an –O-haloalkyl group.

As used herein, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, "heteroarylalkyl" refers to alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, "amino" refers to NH_2.

The term "compound," as used herein, is meant to encompass all stereoisomers, such as enantiomers and diastereomers, all geometric isomers, any tautomeric forms, any isotopic forms, any hydrated forms, and any solvated forms thereof, unless otherwise indicated.

Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active forms, mixtures thereof, or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Isotopic forms include compounds containing various isotopes of the constituent atoms. Isotopes refer to those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. Thus, deuterated and tritiated forms of the compounds described herein are encompassed as are other isotopic forms.

Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include

prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Solvated or hydrated forms of the compounds refer to solid preparations of the compound that include water or solvent molecules. The water or solvent molecules can often be present in a stoichiometric ratio with the compound, and may form part of a crystalline lattice if the compound is in a crystalline form.

As used herein, "substituted" indicates that at least one hydrogen atom of a moiety is replaced by a non-hydrogen substituent or group. When a moiety herein is "substituted," it may have up to the full valance of substitution; for example, methyl can be substituted by 1, 2, or 3 substituents, methylene can be substituted by 1 or 2 substituents, phenyl can be substituted by 1, 2, 3, 4, or 5 substituents, naphthyl can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents, and the like, unless otherwise specified. Likewise, "substituted with one or more substituents" refers to the substitution with one substituent up to the total number of substituents physically allowed. Further, when a moiety is substituted with more than one substituent, the substituents can be identical or they can be different.

In some embodiments, the compounds of the invention, or salts thereof, are isolated. By "isolated" is meant that the compound is at least partially or substantially separated from the environment in which is was formed or discovered. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 90% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art and include, for example, chromatographic methods, distillation, crystallization, and the like.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical

methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present invention also provides prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any covalently bonded carriers which release the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Synthesis

The compounds of the present invention can be prepared in a variety of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given; other process conditions can also be used unless

otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatograpy (HPLC) or thin layer chromatography.

Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

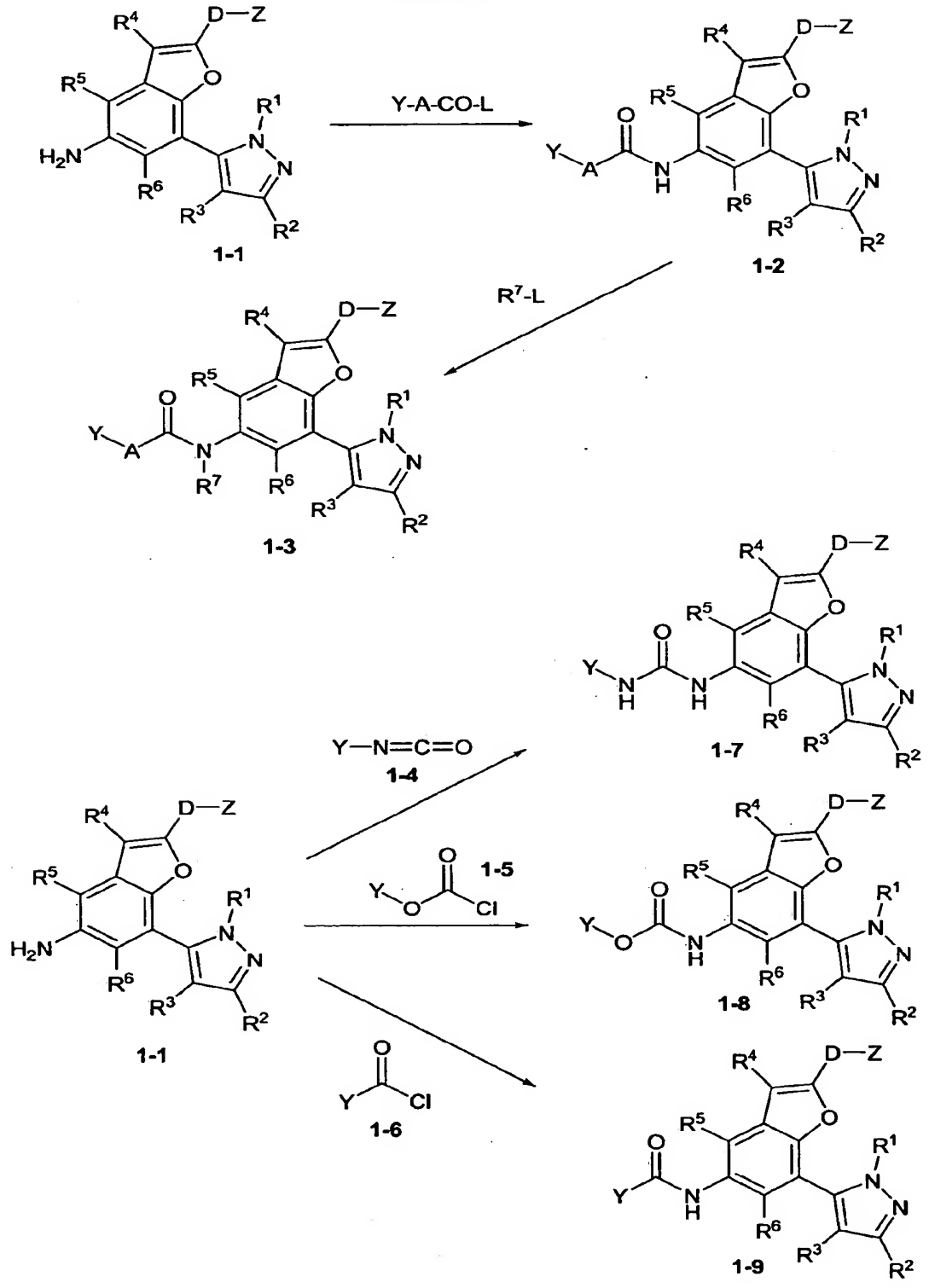
Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids. Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention can be synthesized according to routine methods by those skilled in the art and as shown in the below Schemes.

Scheme 1 depicts a general route to compounds of the invention. For example, amines **1-1** can be coupled with reactants of formula Y-A-CO-L (wherein Y and A are as defined herein, and L is a leaving group such as halo, etc.) to yield amide derivatives **1-2**. The N-atom of the amide group in **1-2** can then be alkylated by routine methods such as by reaction with an alkylating reagent (e.g., R^7-L, wherein R^7 is an alkyl group and L is a leaving group) to give the compounds **1-3**. More particularly, the amine compound **1-1** can be coupled with an isocyanate

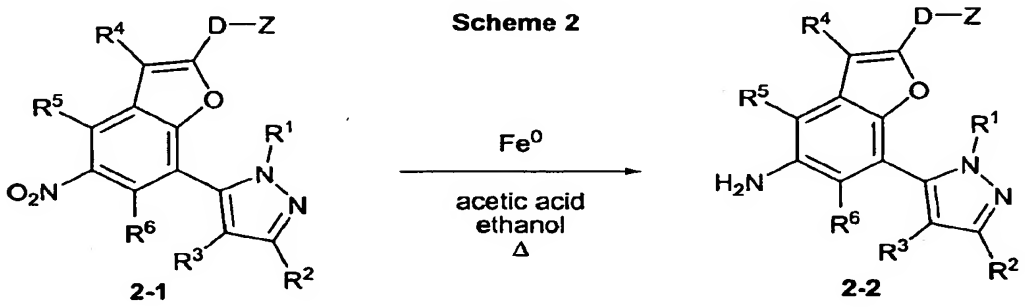
1-4, an orthochloroformate 1-5, or acyl chloride 1-6 to yield their corresponding urea, carbamate, and amide products 1-7, 1-8, and 1-9, respectively.

Scheme 1



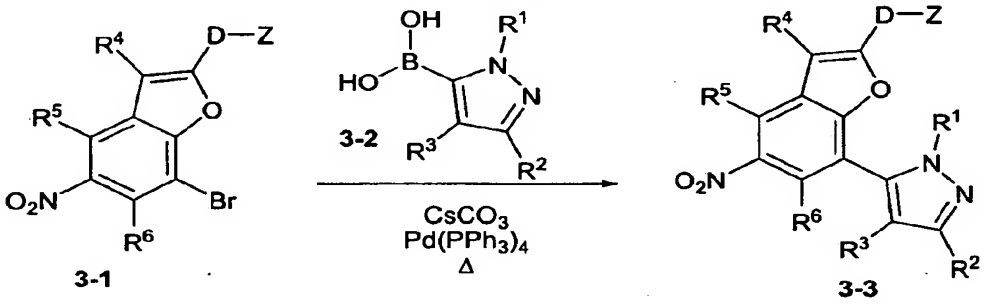
Scheme 2 depicts the preparation of amine intermediates **2-2** which are useful in preparing compounds of the invention (see Scheme 1). For example, nitro compounds **2-1** can be converted to the corresponding amine **2-2** in the presence of a reducing agent such as iron powder in acetic acid/ethanol while heating.

Scheme 2



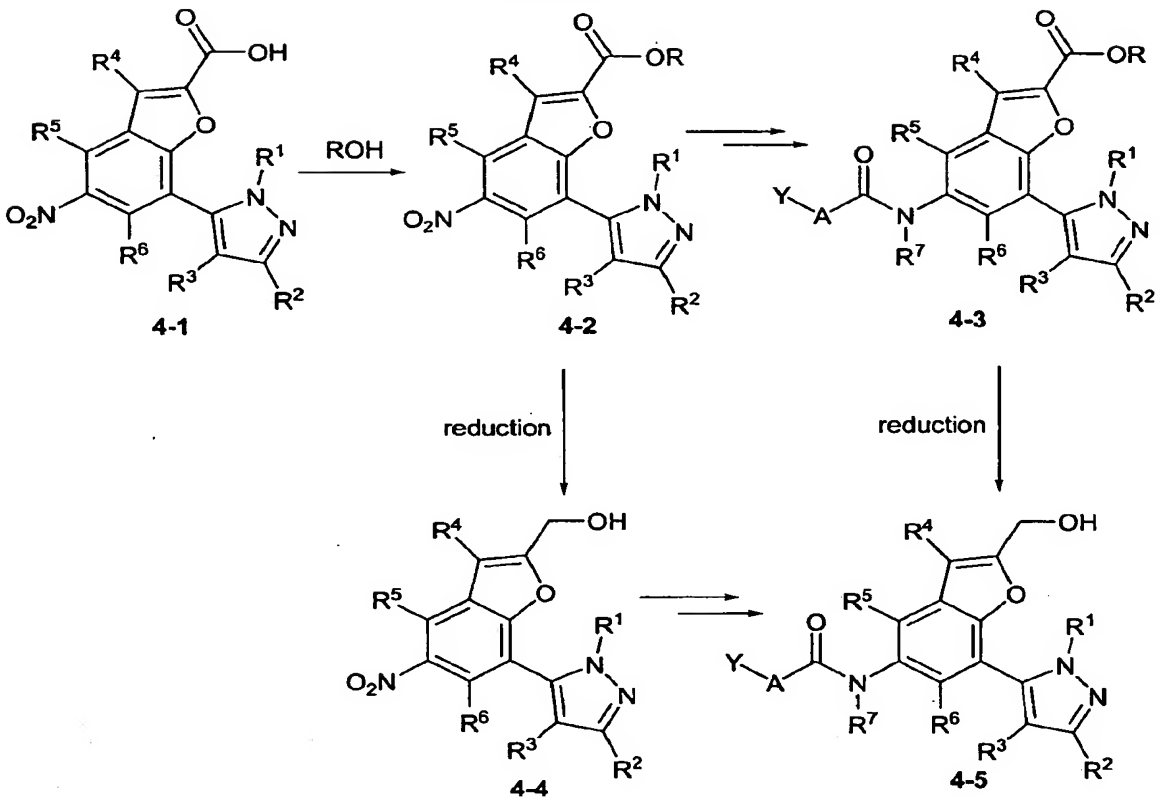
Scheme 3 depicts a synthetic route to 5-(5-nitrobenzofuran-7-yl)-1H-pyrazoles **3-3** which are useful synthetic precursors as illustrated above in Scheme 2. For example, 7-bromo-5-nitrobenzofurans **3-1** can be reacted with pyrazolylboronic acids **3-2** under Suzuki coupling conditions to afford the desired product.

Scheme 3



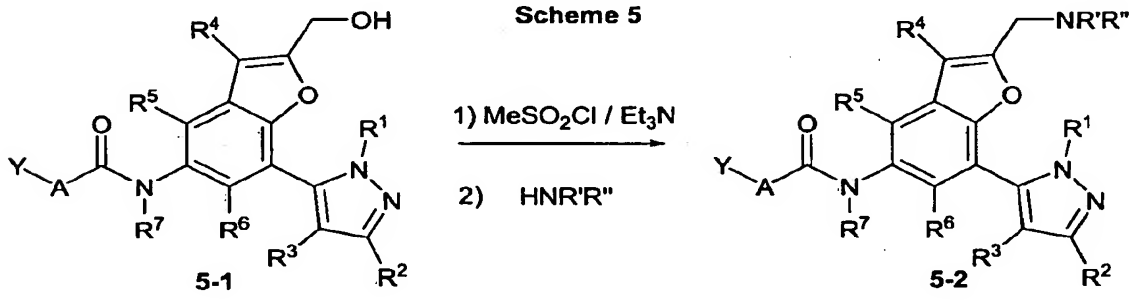
Scheme 4 illustrates example synthetic routes to pyrazole-substituted benzofurans. For example, carboxylic acids **4-1** can be esterified by reaction with alcohols ROH (where R is, for example, alkyl, cycloalkyl, etc.) optionally in the presence of a catalytic amount of acid or base. The resulting ester **4-2** can be transformed to product **4-3** via the routes of Schemes 1 and 2, or reduced with a suitable reducing agent such as DIBAL-H to give the hydroxymethyl compound **4-4**. Ester **4-3** can be treated with a reducing agent in a similar manner to also produce the corresponding hydroxymethyl product **4-5**.

Scheme 4



Scheme 5 illustrates an example synthetic route to further pyrazole-substituted benzofurans. For example, hydroxymethyl compound **5-1** can be converted to heterocycloalkyl-methyl compound **5-2** by first activation of the OH leaving group and then treatment with an amine (e.g., substituted or unsubstituted amine, alkylamine, dialkylamine, cyclic amine, pyrrolidine, piperidine, piperazine, morpholine, azepine, etc.). Such transformations can also be effected on various benzofuran precursors to the compounds of the invention, such as nitro compound **4-4** of Scheme 4 and its corresponding amine.

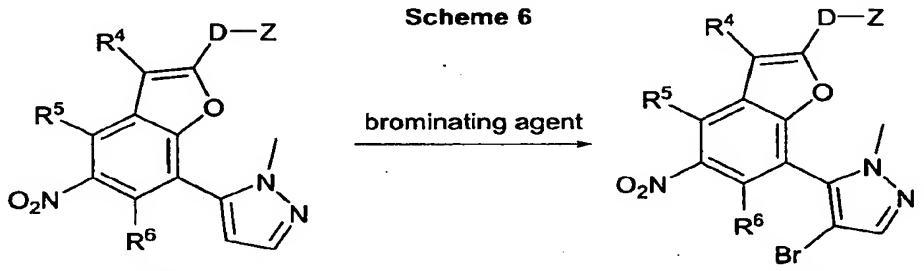
Scheme 5



Scheme 6 illustrates an example method of preparing 4-bromopyrazole compounds 6-2. For example, pyrazole compounds 6-1 can be treated with a brominating agent such as NBS to

afford the desired product. Similarly, other 4-halopyrazole compounds can be prepared by analogous methods with the use of a suitable halogenating agent.

Scheme 6



6-1 6-2

Methods of Use

Compounds of the invention can modulate activity of the 5-HT_{2A} receptor. The term "modulate" is meant to refer to an ability to increase or decrease activity of the receptor. Accordingly, compounds of the invention can be used in methods of modulating the 5-HT_{2A} receptor by contacting the receptor with any one or more of the compounds, salts thereof, or compositions thereof described herein. In some embodiments, compounds of the present invention can act as antagonists (i.e., inhibitors), agonists, or inverse agonists of the 5-HT_{2A} receptor.

The compounds disclosed herein can be useful in the treatment of various diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include conditions related to platelet aggregation, asthma, agitation, schizophrenia, sleep disorders, diabetic-related pathologies, glaucoma, progressive multifocal leukoencephalopathy (PML), hypertension, pain, and the like.

Antiplatelet Therapies (Conditions related to platelet aggregation)

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5-HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see Satimura, K, et al., Clin Cardiol 2002 Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost 1991 Sep 2;66(3):355-60).

5-HT_{2A} inverse agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications (see Br. Med. J. 298: 424 – 430, 1989), Arterial thrombosis (see, Pawlak, D. et al. Thrombosis Research 90: 259 – 270, 1998), atherosclerosis (see, Hayashi, T. et al. Atherosclerosis 168: 23 – 31, 2003), vasoconstriction, caused by serotonin (see, Fujiwara, T. and Chiba, S. Journal of Cardiovascular Pharmacology 26: 503 – 510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. et al. Am Heart J. 145:e16 2003). It can also be used alone or in combination with thrombolytic therapy, for example, tPA (see, Yamashita, T. et al. Haemostasis 30:321 – 332, 2000), to provide cardioprotection following MI or postischemic myocardial dysfunction (see, Muto, T. et al. Mol. Cell. Biochem. 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see, Horibe, E. Circulation Research 68: 68 – 72, 2004), and the like, including complications resulting therefrom.

5-HT_{2A} inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and artherosclerosis (see Nomura, Shosaku, et al. Blood Coagulation and Fibrinolysis 2005, *16*, 423-428).

The 5-HT_{2A} inverse agonists disclosed herein can provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof comprising administering to the patient a composition comprising a compound of the invention which is a 5-HT_{2A} inverse agonist. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist of the invention.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

Asthma

5-HT (5-hydroxytryptamine) has been linked to the pathophysiology of acute asthma (see Cazzola, M. and Matera, M.G., TIPS, 2000, 21, 13; and De Bie, J.J. et al., British J. Pharm., 1998, 124, 857-864). The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a compound of the invention which is a 5-HT_{2A} inverse agonist. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

Agitation

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. *J* Am Geriatr Soc 34(10): 711-721).

Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are

degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(suppl 2):S45-S50).

An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia; of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia.

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., *J* Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976).

The compounds of the invention disclosed herein can be useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to the patient a composition comprising a compound of the invention which is 5-HT_{2A} inverse agonist. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimers disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including, without limitation, stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

Add-On therapy to Haloperidol in the treatment of schizophrenia and other disorders

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders

of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (*See*, American Statistical and Diagnostic Handbook).

Haloperidol (Haldol) is a potent dopamine D_2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5-HT_{2A} inverse agonist concomitantly with Haldol can provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of compounds of the invention which are 5-HT_{2A} inverse agonists with haloperidol also will provide benefits in these indications.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient a dopamine D_2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine D_2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for treating schizophrenia in a patient in need of the treatment comprising administering to the patient a dopamine D_2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D_2 receptor antagonist is haloperidol.

The administration of the dopamine D_2 receptor antagonist can be concomitant with administration of the 5-HT_{2A} inverse agonist, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the 5-HT_{2A} inverse agonist are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from schizophrenia, comprising administering to the patient a 5-HT_{2A} inverse agonist as disclosed herein.

Sleep disorders

It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, more than one-half of the adults surveyed (58%) report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, about three in ten (35%) say they have experienced insomnia-like symptoms every night or almost every night.

The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of Sleep Disorders, there are over 80 recognized sleep disorders. Of these, compounds of the present invention are effective, for example, in any one or more of the following sleep disorders (ICSD – International Classification of Sleep Disorders: Diagnostic and Coding Manual. *Diagnostic Classification Steering Committee,* American Sleep Disorders Association, 1990): dyssomnias, parasomnias, sleep disorders associated with medical/psychiatric disorders, and the like.

A. DYSSOMNIAS

a. Intrinsic Sleep Disorders:

Psychophysiological insomnia, Sleep state misperception, Idiopathic insomnia, Obstructive sleep apnea syndrome, Central sleep apnea syndrome, Central alveolar hypoventilation syndrome, Periodic limb movement disorder, Restless leg syndrome and Intrinsic sleep disorder NOS.

b. Extrinsic Sleep Disorders:

Inadequate sleep hygiene, Environmental sleep disorder, Altitude insomnia, Adjustment sleep disorder, Insufficient sleep syndrome, Limit-setting sleep disorder, SleepOnset association disorder, Nocturnal eating (drinking) syndrome, Hypnotic dependent sleep disorder, Stimulant-

dependent sleep disorder, Alcohol-dependent sleep disorder, Toxin-induced sleep disorder and Extrinsic sleep disorder NOS.

c. Circadian Rhythm Sleep Disorders:

Time zone change (jet lag) syndrome, Shift work sleep disorder, Irregular sleep-wake pattern, Delayed sleep phase syndrome, Advanced sleep phase syndrome, Non-24-hour sleep-wake disorder and Circadian rhythm sleep disorder NOS.

B. PARASOMNIAS

a. Arousal Disorders:

Confusional arousals, Sleepwalking and Sleep terrors.

b. Sleep-Wake Transition Disorders:

Rhythmic movement disorder, Sleep starts, Sleep talking and Nocturnal leg cramps.

C. SLEEP DISORDERS ASSOCIATED WITH MEDICAL/PSYCHIATRIC DISORDERS

a. Associated with Mental Disorders:

Psychoses, Mood disorders, Anxiety disorders, Panic disorders and Alcoholism.

b. Associated with Neurological Disorders:

Cerebral degenerative disorders, Dementia, Parkinsonism, Fatal familial insomnia, Sleep-related epilepsy, Electrical status epilepticus of sleep and Sleep-related headaches.

c. Associated with Other Medical Disorders:

Sleeping sickness, Nocturnal cardiac ischemia, Chronic obstructive pulmonary disease, Sleep-related asthma, Sleep-related gastroesophageal reflux, Peptic ulcer disease, Fibrositis syndrome, Osteoarthritis, Rheumatoid arthritis, Fibromyalgia and Post-surgical.

The effects of sleep deprivation are more than excessive daytime sleepiness. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung, and Blood Institute, *Insomnia Facts Sheet*, Oct. 1995). Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction, compromised glucose tolerance, increased obesity and metabolic syndrome. Compounds of the present invention are useful to prevent or alleviate these complications by improving sleep quality.

The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over

drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used. In addition, benzodiazepines are used to induce sleep, but have little to no effect on the maintenance of sleep, sleep consolidation or slow wave sleep. Therefore, sleep maintenance disorders are not currently well treated.

Clinical studies with agents of a similar mechanism of action, as are compounds of the present invention, have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpley AL, et al. Slow Wave Sleep in Humans: Role of 5-HT_{2A} and $5HT_{2C}$ Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4):467-71; Winokur A, et al. Acute Effects of Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc of Biol Psych,* 2000, Vol. 48:75-78; and Landolt HP, et al. Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology,* 1999, Vol. 21(3):455-66].

Some sleep disorders are sometimes found in conjunction with other conditions and accordingly those conditions are treatable by compounds of Formula I. For example, but not limited to, patients suffering from mood disorders typically suffer from a sleep disorder that can be treatable by compounds of Formula I. Having one pharmacological agent which treats two or more existing or potential conditions, as does the present invention, is more cost effective, leads to better compliance and has fewer side effects than taking two or more agents.

In some embodiments, the present invention provides a therapeutic agent for the use in treating Sleep Disorders. In further embodiments, the present invention provides one pharmaceutical agent, which can be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. In yet further embodiment, compounds of the present invention described herein can be used alone or in combination with a mild sleep inducer (i.e. antihistamine).

Sleep Architecture:

Sleep comprises two physiological states: Non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. So called delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning the patient spends a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. As used herein, the term "fragmented sleep architecture" means an individual, such as a sleep disorder patient, spends the majority of their sleep time in NREM sleep stages 1 and 2, lighter periods of sleep from which the individual can be easily aroused to a Waking

state by limited external stimuli. As a result, the individual cycles through frequent bouts of light sleep interrupted by frequent awakenings throughout the sleep period. Many sleep disorders are characterized by a fragmented sleep architecture. For example, many elderly patients with sleep complaints have difficulty achieving long bouts of deep refreshing sleep (NREM stages 3 and 4) and instead spend the majority of their sleep time in NREM sleep stages 1 and 2.

In contrast to fragmented sleep architecture, as used herein the term "sleep consolidation" means a state in which the number of NREM sleep bouts, particularly Stages 3 and 4, and the length of those sleep bouts are increased, while the number and length of waking bouts are decreased. In essence, the architecture of the sleep disorder patient is consolidated to a sleeping state with increased periods of sleep and fewer awakenings during the night and more time is spent in slow wave sleep (Stages 3 and 4) with fewer oscillation Stage 1 and 2 sleep. Compounds of the present invention can be effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall, and muscles relax. In normal sleep architecture, NREM sleep makes up about 75% of total sleep time; stage 1 accounting for 5-10% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 12%, and stage 4 13-15%. About 90 minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night. REM makes up approximately 25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration, and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as "paradoxical sleep." Sleep onset occurs during NREM sleep and takes 10-20 minutes in healthy young adults. The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable; a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods may last up to 40 minutes. With aging, the time between retiring and sleep onset increases and the total amount of night-time sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

As used herein, the term "delta power" means a measure of the duration of EEG activity in the 0.5 to 3.5 Hz range during NREM sleep and is thought to be a measure of deeper, more refreshing sleep. Delta power is hypothesized to be a measure of a theoretical process called Process S and is thought to be inversely related to the amount of sleep an individual experiences during a given sleep period. Sleep is controlled by homeostatic mechanisms; therefore, the less

one sleeps the greater the drive to sleep. It is believed that Process S builds throughout the wake period and is discharged most efficiently during delta power sleep. Delta power is a measure of the magnitude of Process S prior to the sleep period. The longer one stays awake, the greater Process S or drive to sleep and thus the greater the delta power during NREM sleep. However, individuals with sleep disorders have difficulty achieving and maintaining delta wave sleep, and thus have a large build-up of Process S with limited ability to discharge this buildup during sleep. 5-HT_{2A} agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT_{2A} inverse agonist or antagonist will be able to achieve deeper more refreshing sleep. These same effects have not been observed with currently marketed pharmacotherapies. In addition, currently marketed pharmacotherapies for sleep have side effects such as hangover effects or addiction that are associated with the GABA receptor. 5-HT_{2A} inverse agonists usually do not target the GABA receptor and so these side effects are not typically a concern.

Subjective and objective determinations of sleep disorders:

There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times does the patient wake up during the night, how restless is the patient during sleep, etc. Another method is to objectively measure the stages of sleep using polysomnography.

Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electroculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

In addition, the compounds of the invention can be useful for the treatment of the sleep disorders characterized by excessive daytime sleepiness such as narcolepsy. Inverse agonists at the serotonin 5-HT_{2A} receptor improve the quality of sleep at nightime which can decrease excessive daytime sleepiness.

Accordingly, another aspect of the present invention relates to the therapeutic use of compounds of the present invention for the treatment of Sleep Disorders. Compounds of the present invention are potent inverse agonists at the serotonin 5-HT_{2A} receptor and can be effective in the treatment of Sleep Disorders by promoting one or more of the following: reducing the sleep onset latency period (measure of sleep induction), reducing the number of nighttime awakenings, and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement and sleep consolidation) without effecting REM sleep. In addition, compounds of the present invention can be effective either as a monotherapy or in combination with sleep inducing agents, for example but not limited to, antihistamines.

Diabetic-Related Pathologies

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), increased plasma serotonin concentration in diabetic patients has also been implicated to play a role in disease progression (Pietraszek, M.H., et al. *Thrombosis Res.* 1992, 66(6), 765-74; and Andrzejewska-Buczko J, et al., *Klin Oczna.* 1996; 98(2), 101-4). Serotonin is believed to play a role in vasospasm and increased platelet aggregability. Improving microvascular blood flow is able to benefit diabetic complications.

A recent study by Cameron and Cotter in *Naunyn Schmiedebergs Arch Pharmacol.* 2003 Jun; 367(6):607-14, used a 5-HT_{2A} antagonist experimental drug AT-1015, and other non-specific 5-HT_{2A} antagonists including ritanserin and sarpogrelate. These studies found that all three drugs were able to produce a marked correction (82.6-99.7%) of a 19.8% sciatic motor conduction deficit in diabetic rats. Similarly, 44.7% and 14.9% reductions in sciatic endoneurial blood flow and saphenous sensory conduction velocity were completely reversed.

In a separate patient study, sarogrelate was evaluated for the prevention of the development or progression of diabetic nephropathy (Takahashi, T., et al., *Diabetes Res Clin Pract.* 2002 Nov; 58(2):123-9). In the trial of 24 months of treatment, sarpogrelate significantly reduced urinary albumin excretion level.

Glaucoma

Topical ocular administration of 5-HT2 receptor antagonists result in a decrease in intra ocular pressure (IOP) in monkeys (Chang et al., *J. Ocul Pharmacol* 1:137-147 (1985)) and humans (Mastropasqua et al., *Acta Ophthalmol Scand Suppl* 224:24-25 (1997)) indicating utility for similar compounds such as 5-HT_{2A} inverse agonists in the treatment of ocular hypertension associated with glaucoma. The 5-HT2 receptor antagonist ketanserin (Mastropasqua supra) and sarpogrelate (Takenaka et al., *Investig Ophthalmol Vis Sci* 36:S734 (1995)) have been shown to significantly lower IOP in glaucoma patients.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a lethal demyelinating disease caused by an opportunistic viral infection of oligodendrocytes in immunocompromised patients. The causative agent is JC virus, a ubiquitous papovavirus that infects the majority of the population before adulthood and establishes a latent infection in the kidney. In immunocompromised hosts, the virus can reactivate and productively infect oligodendrocytes. This previously rare condition, until 1984 reported primarily in persons with underlying lymphoproliferative disorders, is now more common because it occurs in 4% of patients with AIDS. Patients usually present with relentlessly progressive focal neurologic defects, such as hemiparesis or visual field deficits, or with alterations in mental status. On brain MRI, one or more white matter lesions are present; they are hyperintense on T2-weighted images and hypointense on T1-weighted images. There is no mass effect, and contrast enhancement is rare. Diagnosis can be confirmed by brain biopsy, with demonstration of virus by *in situ* hybridization or immunocytochemistry. Polymerase chain reaction amplification of JC virus sequences from the CSF can confirm diagnosis without the need for biopsy [*see*, e.g., Antinori et al., *Neurology* (1997) 48:687-694; Berger and Major, *Seminars in Neurology* (1999) 19:193-200; *and* Portegies, et al., *Eur. J. Neurol.* (2004) 11:297-304]. Currently, there is no effective therapy. Survival after diagnosis is about 3 to 5 months in AIDS patients.

JC virus enters cells by receptor-mediated clathrin-dependent endocytosis. Binding of JC virus to human glial cells (*e.g.*, oligodendrocytes) induces an intracellular signal that is critical for entry and infection by a ligand-inducible clathrin-dependent mechanism [Querbes et al., *J Virology* (2004) 78:250-256]. Recently, 5-HT_{2A} was shown to be the receptor on human glial cells mediating infectious entry of JC virus by clathrin-dependent endocytosis [Elphick et al., *Science*

(2004) 306:1380-1383]. 5-HT_{2A} antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT_{2A}.

5-HT_{2A} antagonists including inverse agonists have been contemplated to be useful in the treatment of PML [Elphick et al., *Science* (2004) 306:1380-1383]. Prophylactic treatment of HIV-infected patients with 5-HT_{2A} antagonists is envisioned to prevent the spread of JC virus to the central nervous system and the development of PML. Aggressive therapeutic treatment of patients with PML is envisioned to reduce viral spread within the central nervous system and prevent additional episodes of demyelination.

In some embodiments, methods are provided for treating progressive multifocal leukoencephalopathy in a patient in need of such treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

Hypertension

Serotonin has been observed to play an important role in the regulation of vascular tone, vasoconstriction, and pulmonary hypertension (see, Deuchar, G. et al. Pulm. Pharmacol. Ther. 18(1):23-31. 2005; and Marcos, E. et al. Circ. Res. 94(9):1263-70 2004). Ketanserin, a 5-HT_{2A} inverse agonist, has been demonstrated to protect against circulatory shocks, intracranial hypertension, and cerebral ischemia during heatstroke (see, Chang, C. et al. Shock 24(4): 336-340 2005); and to stabilize blood pressure in spontaneously hypertensive rats (see, Miao, C. Clin. Exp. Pharmacol. Physiol. 30(3): 189-193). Mianserin, a 5-HT_{2A} inverse agonist, has been shown to prevent DOCA-salt induced hypertension in rats (see, Silva, A. Eur, J. Pharmacol. 518(2-3): 152-7 2005).

Pain

5-HT_{2A} inverse agonists are also effective for the treatment of pain. Sarpogrelate has been observed to provide a significant analgesic effect both on thermal induced pain in rats after intraperitoneal administration and on inflammatory pain in rats after either intrathecal or intraperitoneal administration (see, Nishiyama, T. Eur. J. Pharmacol. 516:18-22 2005). This same 5-HT_{2A} inverse agonist in humans has been shown to be an effective treatment for lower back pain, leg pain and numbness associated with sciatica brought on by lumbar disc herniation (see, Kanayama, M. et al. J. Neurosurg: Spine 2:441-446 2005).

One aspect of the present invention encompasses methods for modulating the activity of a 5-HT_{2A} serotonin receptor by contacting the receptor with a compound according to any of the

embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of platelet aggregation in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of an indication selected from coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of reducing the risk of blood clot formation in a patient undergoing an angioplasty or coronary bypass surgery comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of reducing the risk of blood clot formation in a patient suffering from atrial fibrillation, comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of asthma in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of a symptom of asthma in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

One aspect of the present invention encompasses methods for the treatment of agitation or a symptom thereof in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the patient is a cognitively intact elderly patient.

One aspect of the present invention encompasses methods for the treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the

patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the dementia is due to a degenerative disease of the nervous system. In some embodiments, the dementia is Alzheimers disease, Lewy Body, Parkinson's disease or Huntington's disease. In some embodiments, the dementia is due to diseases that affect blood vessels. In some embodiments, the dementia is due to stroke or multi-infarct dementia.

One aspect of the present invention encompasses methods for the treatment of a patient suffering from at least one of the indications selected from behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D_2 receptor antagonist and a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the dopamine D_2 receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for the treatment of a patient with infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D_2 receptor antagonist and a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the dopamine D_2 receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for the treatment of schizophrenia in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a dopamine D_2 receptor antagonist and a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the dopamine D_2 receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for the treatment of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from the schizophrenia, comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition. In some embodiments, the haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms. In some embodiments, the haloperidol and the compound, pharmaceutically acceptable salt thereof, or pharmaceutical composition are administered in a single dosage form.

One aspect of the present invention encompasses methods for the treatment of a sleep disorder in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

In some embodiments, the sleep disorder is a dyssomnia. In some embodiments, the dyssomnia is selected from the group consisting of psychophysiological insomnia, sleep state misperception, idiopathic insomnia, obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome, periodic limb movement disorder, restless leg syndrome, inadequate sleep hygiene, environmental sleep disorder, altitude insomnia, adjustment sleep disorder, insufficient sleep syndrome, limit-setting sleep disorder, sleep-onset association disorder, nocturnal eating or drinking syndrome, hypnotic dependent sleep disorder, stimulant-dependent sleep disorder, alcohol-dependent sleep disorder, toxin-induced sleep disorder, time zone change (jet lag) syndrome, shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, and non-24-hour sleep-wake disorder.

In some embodiments, the sleep disorder is a parasomnia. In some embodiments, the parasomnia is selected from the group consisting of confusional arousals, sleepwalking and sleep terrors, rhythmic movement disorder, sleep starts, sleep talking and nocturnal leg cramps. In some embodiments, the sleep disorder is characterized by excessive daytime sleepiness such as narcolepsy.

In some embodiments, the sleep disorder is associated with a medical or psychiatric disorder. In some embodiments, the medical or psychiatric disorder is selected from the group consisting of psychoses, mood disorders, anxiety disorders, panic disorders, alcoholism, cerebral degenerative disorders, dementia, parkinsonism, fatal familial insomnia, sleep-related epilepsy, electrical status epilepticus of sleep, sleep-related headaches, sleeping sickness, nocturnal cardiac ischemia, chronic obstructive pulmonary disease, sleep-related asthma, sleep-related gastroesophageal reflux, peptic ulcer disease, fibrositis syndrome, osteoarthritis, rheumatoid arthritis, fibromyalgia and post-surgical sleep disorder.

One aspect of the present invention encompasses methods for the treatment of a diabetic-related disorder in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

In some embodiments, the diabetic-related disorder is diabetic peripheral neuropathy.

In some embodiments, the diabetic-related disorder is diabetic nephropathy.

In some embodiments, the diabetic-related disorder is diabetic retinopathy.

One aspect of the present invention encompasses methods for the treatment of glaucoma or other diseases of the eye with abnormal intraocular pressure.

One aspect of the present invention encompasses methods for the treatment of progressive multifocal leukoencephalopathy in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein, pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

In some embodiments, the individual in need thereof has a lymphoproliferative disorder. In some embodiments, the lymphoproliferative disorder is leukemia or lymphoma. In some embodiments, the leukemia or lymphoma is chronic lymphocytic leukemia, Hodgkin's disease, or the like.

In some embodiments, the patient in need thereof has a myeloproliferative disorder.

In some embodiments, the patient in need thereof has carcinomatosis.

In some embodiments, the patient in need thereof has a granulomatous or inflammatory disease. In some embodiments, the granulomatous or inflammatory disease is tuberculosis or sarcoidosis.

In some embodiments, the patient in need thereof is immunocompromised. In some embodiments, the immunocompromised patient has impaired cellular immunity. In some embodiments, the impaired cellular immunity comprises impaired T-cell immunity.

In some embodiments, the patient in need thereof is infected with HIV. In some embodiments, the HIV-infected patient has a CD4+ cell count of $\leq 200/mm^3$. In some embodiments, the HIV-infected patient has AIDS. In some embodiments, the HIV-infected patient has AIDS-related complex (ARC). In certain embodiments, ARC is defined as the presence of two successive CD4+ cell counts below $200/mm^3$ and at least two of the following signs or symptoms: oral hairy leukoplakia, recurrent oral candidiasis, weight loss of at least 2.5 kg or 10% of body weight within last six months, multidermatomal herpes zoster, temperature above 38.5°C for more than 14 consecutive days or more than 15 days in a 30-day period, or diarrhea with more than three liquid stools per day for at least 30 days [*see*, e.g., Yamada et al., *Clin. Diagn. Virol.* (1993) 1:245-256].

In some embodiments, the patient in need thereof is undergoing immunosuppressive therapy. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent [*see*, e.g., Mueller, *Ann Thorac Surg* (2004) 77:354-362; and Krieger and Emre, *Pediatr Transplantation* (2004) 8:594-599]. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent selected from the group consisting of: corticosteroids (for example, prednisone and the like), calcineurin inhibitors (for example, cyclosporine, tacrolimus, and the like), antiproliferative agents (for example, azathioprine, mycophenolate mofetil, sirolimus, everolimus, and the like), T-cell depleting agents (for example, OKT®3 monoclonal antibody (mAb), anti-CD3 immunotoxin FN18-CRM9, Campath-1H (anti-CD52) mAb, anti-CD4 mAb, anti-T cell receptor mAb, and the

like), anti-IL-2 receptor (CD25) mAb (for example, basiliximab, daclizumab, and the like), inhibitors of co-stimulation (for example, CTLA4-Ig, anti-CD154 (CD40 ligand) mAb, and the like), deoxyspergualin and analogs thereof (for example, 15-DSG, LF-08-0299, LF14-0195, and the like), leflunomide and analogs thereof (for example, leflunomide, FK778, FK779, and the like), FTY720, anti-alpha-4-integrin monoclonal antibody, and anti-CD45 RB monoclonal antibody. In some embodiments, the immunosuppressive agent and said compound or pharmaceutical composition are administered in separate doseage forms. In some embodiments, the immunosuppressive agent and said compound or pharmaceutical composition are administered in a single dosage form.

In some embodiments, the patient in need thereof is undergoing immunosuppressive therapy after organ transplantation. In some embodiments, the organ is liver, kidney, lung, heart, or the like [see, e.g., Singh et al., *Transplantation* (2000) 69:467-472].

In some embodiments, the patient in need thereof is undergoing treatment for a rheumatic disease. In some embodiments, the rheumatic disease is systemic lupus erythematosus or the like.

In some embodiments, the compound or the pharmaceutical composition inhibits JC virus infection of human glial cells.

One aspect of the present invention encompasses processes for preparing a composition comprising admixing a compound according any embodiments described herein and pharmaceutically acceptable carrier.

One aspect of the present invention is the use of a compound of the invention, pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, for the production of a medicament for use in the treatment of a 5-HT_{2A} related disorder.

One aspect of the present invention is the use of a compound of the invention, pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof for the treatment of a 5-HT_{2A} related disorder.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the 5-HT_{2A} receptor with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a 5-HT_{2A} receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the 5-HT_{2A} receptor.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "in need of treatment" or "in need thereof" refers to a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

The term, "agonist" is meant to refer to a moiety that interacts with and activates the receptor, such as the 5-HT_{2A} receptor, and initiates a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term, "antagonist" is meant to refer to a moiety that competitively binds to the receptor at the same site as an agonist (for example, the endogenous ligand), but which does not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term, "inverse agonist" refers to a moiety that binds the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibits the baseline

intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decreases GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

Combination Therapy

While the compounds of the present invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), they can also be used in combination with other pharmaceutical agents (i.e., combination-therapy) for the treatment of any one or more of the diseases/conditions/disorders described herein. Accordingly, the present invention includes methods of treatment of 5-HT_{2A} serotonin receptor related disorders or diseases comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of the present invention, or pharmaceutically acceptable salt thereof, in combination with one or more additional pharmaceutical agents as described herein.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include other antiplatelet, antithrombotic or anticoagulant drugs, anti-arrhythmic agents, Cholesteryl ester transfer protein (CETP) inhibitors, Niacin or niacin analogs, Adenosine or adenosine analogs, Nitroglycerin or nitrates, prothrombolytic agents, and the like. Other pharmaceutical agents, including the agents set forth *infra*, are well known or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

The compounds of the present invention can also be used in combination with other antiplatelet, antithrombotic or anticoagulant drugs such as thrombin inhibitors, platelet aggregation inhibitors such as aspirin, clopidogrel (Plavix®), ticlopidine or CS-747 {i.e., acetic acid 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl ester and its active metabolite *R*-99224, (Z)-2-[1-[2-cyclopropyl-1(*S*)-(2-fluorophenyl)-2-oxoethyl]-4(*R*)-sulfanylpiperidin-3-ylidene]acetic acid}, abciximab (ReoPro®), eptifibatide (Integrilin®), tirofiban (Aggrastat®), warfarin, low molecular weight heparins (such as LOVENOX), GPIIb/GPIIIa blockers, PAI-1 inhibitors such as XR-330 [i.e., (3*Z*,6*Z*)-3-Benzylidene-6-(4-methoxybenzylidene)-1-methylpiperazine-2,5-dione] and T-686 [i.e., 3(*E*)-Benzylidene-4(*E*)-(3,4,5-trimethoxybenzylidene)pyrrolidine-2,5-dione], inhibitors of α-2-antiplasmin such as anti-α-2-antiplasmin antibody and thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, phosphodiesterase (PDE) inhibitors, such as dipyridamole (Persantine®) or cilostazol, PDE inhibitors in combination with thromboxane receptor antagonists/thromboxane A synthetase inhibitors (such as picotamide), serotonin-2-receptor antagonists (such as ketanserin), fibrinogen receptor antagonists, hypolipidemic agents, such as HMG-CoA reductase inhibitors, e.g., pravastatin, simvastatin, atorvastatin, fluvastatin,

cerivastatin, AZ4522, and itavastatin (Nissan/Kowa); microsomal triglyceride transport protein inhibitors (such as disclosed in U.S. Pat. Nos. 5,739,135, 5,712,279 and 5,760,246), antihypertensive agents such as angiotensin-converting enzyme inhibitors (e.g., captopril, lisinopril or fosinopril); angiotensin-II receptor antagonists (e.g., irbesartan, losartan or valsartan); and/or ACE/NEP inhibitors (e.g., omapatrilat and gemopatrilat); β-blockers (such as propranolol, nadolol and carvedilol), PDE inhibitors in combination with aspirin, ifetroban, picotamide, ketanserin, or clopidogrel (Plavix®) and the like.

The compounds of the present invention can also be used in combination with anti-arrhythmic agents such as for atrial fibrillation, for example, amiodarone or dofetilide.

The compounds of the present invention can also be used in combination with Cholesteryl ester transfer protein (CETP) inhibitors for dislipidemia and atherosclerosis, Niacin or niacin analogs for dislipidemia and atherosclerosis, Adenosine or adenosine analogs for vasodilation, Nitroglycerin or nitrates for vasodilation.

The compounds of the present invention can be used in combination with prothrombolytic agents, such as tissue plasminogen activator (natural or recombinant), streptokinase, reteplase, activase, lanoteplase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, and the like. The compounds of the present invention may also be used in combination with β-adrenergic agonists such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, or fenoterol; anticholinergics such as ipratropium bromide; anti-inflammatory cortiocosteroids such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide or dexamethasone; and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, monteleukast and pranleukast.

Suitable pharmaceutical agents that can be used in combination with compounds of the present invention include antiretrovirals [*see*, e.g., Turpin, *Expert Rev Anti Infect Ther* (2003) 1:97-128]. Some embodiments of the present invention include methods of treatment of progressive multifocal leukoencephalopathy as described herein comprising administering to an individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: nucleoside reverse transcriptase inhibitors (for example, Retrovir®, Epivir®, Combivir®, Hivid®, Videx®, Trizvir®, Zerit®, Ziagen®, Vired®, Emtricitabine, DAPD, and the like), non-nucleoside reverse transcriptase inhibitors (for example, Virammune®, Rescriptor®, Sustiva®, GW687, DPC083, TMC 125, Emivirine, Capravirine, BMS 561390, UC-781 and other oxathiin carboxyanilides, SJ-3366, Alkenyldiarylmethane (ADAM), Tivirapine, Calanolide A, HBY097, Loviride, HEPT Family Derivatives, TIBO Derivatives, and the like), protease inhibitors (for example, Fortovase®, Invirase®, Novir®, Crixivan®, Viracep®, Ageberase®, Kaletra®, Atazanavir, Tipranavir, DMP450, and the like), inhibitors of HIV-cell

interaction (for example, soluble CD4, toxin-conjugated CD4, monoclonal antibodies to CD4 or gp120, PRO 542, dextran sulfate, Rersobene, FP-23199, Cyanovirin-N, Zintevir (T30177, AR177), L-chicoric acid and derivatives, and the like), coreceptor inhibitors ligands (for example, R5, X4, modified ligands (R5), modified ligands (X4), and the like), coreceptor inhibitors X4 (for example, T22, T134, ALX40-4C, AMD3100, bycyclam derivatives, and the like), coreceptor inhibitors R5 (for example, TAK-779, SCH-C (SCH-351125), SCH-D (SCH-350634), NSC 651016, ONO Pharmaceutical, Merck, and the like), fusion inhibitors (for example, Fuzeon® (T-20, DP 178, enfuvritide) trimeris, T-1249, TMC125, and the like), integrase inhibitors (for example, 5CITEP, L731,988, L708,906, L-870,812, S-1360, and the like), NCp7 nucleocapsid Zn finger inhibitors (for example, NOBA, DIBA, dithianes, PD-161374, pyridinioalkanoyl thioesters (PATES), azodicarbonamide (ADA), cyclic 2,2 dithio bisbenzamide, and the like), RNase H inhibitors (for example, BBHN, CPHM PD-26388, and the like), Tat inhibitors (for example, dominant negative mutants, Ro24-7429, Ro5-3335, and the like), Rev inhibitors (for example, dominant negative mutants, Leptomycin B, PKF050-638, and the like), transcriptional inhibitors (for example, Temacrazine, K-12 and K-37, EM2487, and the like), inhibitors of HIV assembly/maturation (for example, CAP-1 and CAP-2, and the like), and pharmaceutical agents directed to cellular anti-HIV targets (for example, LB6-B275 and HRM1275, Cdk9 inhibitors, and the like).

In a certain embodiment, a compound of the invention can be used in conjunction with highly active antiretroviral therapy (HAART). When antiretroviral drugs are used in combinations of three or four drugs, this treatment is called HAART [*see*, e.g., Portegies, et al., *Eur. J. Neurol.* (2004) 11:297-304].

In accordance with the present invention, the combination of a compound of the present invention and pharmaceutical agent can be prepared by mixing the respective active components either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, diluent, etc., and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition(s). When one or more compounds of the invention, or pharmaceutically acceptable salts thereof, are administered as a combination therapy with another active compound, each can be formulated as separate pharmaceutical compositions given at the same time or at different times. Alternatively, in some embodiments, pharmaceutical compositions of the present invention comprise one or more compounds of the invention, or pharmaceutically acceptable salts thereof, and one or more further pharmaceutical agent(s) as a single pharmaceutical composition.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention, or pharmaceutically acceptable salts thereof, can be administered in the form of a pharmaceutical

composition which is a combination of at least one compound of the invention, or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10 % by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The

compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions of the present invention can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral adminstration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of

the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compounds of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to fluorescent dye, spin label, heavy metal or radio-labeled compounds of the invention that would be useful not only in imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the receptor in tissue samples, including human, and for identifying receptor ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes receptor assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* IDO enzyme labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I, ^{35}S and ^{82}Br.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radio-labeled compound of the invention to the receptor. Accordingly, the ability of a test compound to

compete with the radio-labeled compound for binding to the IDO enzyme directly correlates to its binding affinity.

Kits

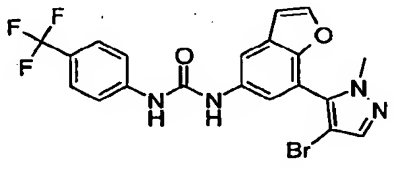
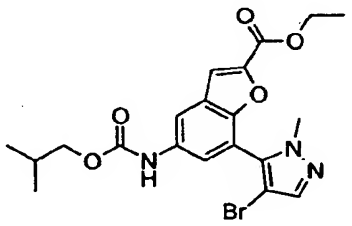
The present invention also includes pharmaceutical kits useful, for example, in the treatment of 5-HT_{2A} related diseases or disorders referred to herein which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention or pharmaceutically acceptable salt thereof. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

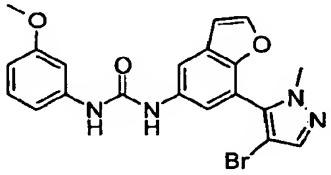
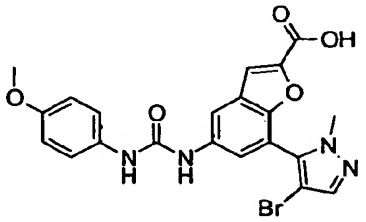
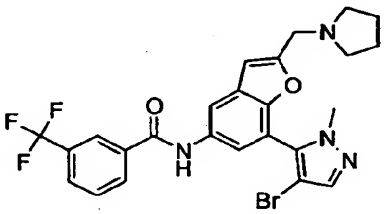
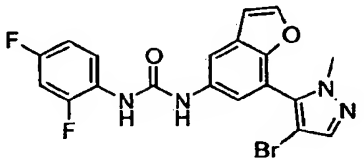
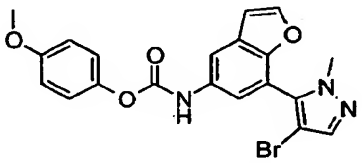
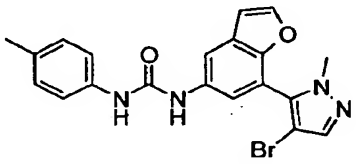
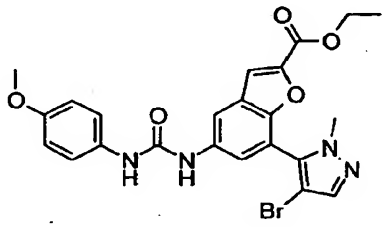
The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

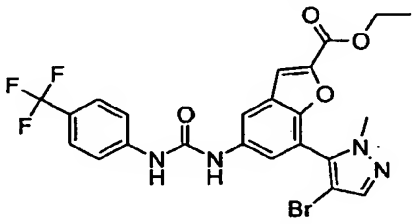
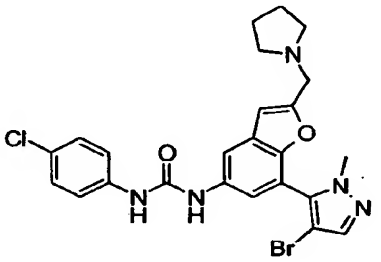
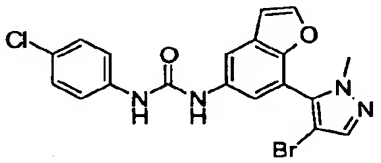
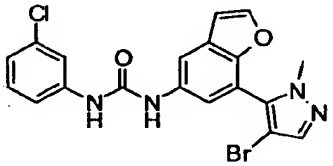
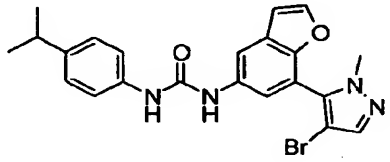
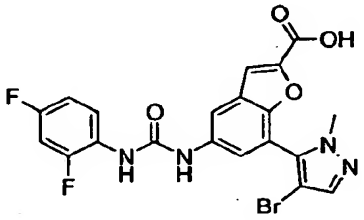
EXAMPLES

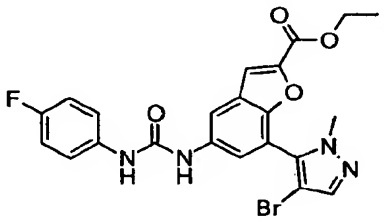
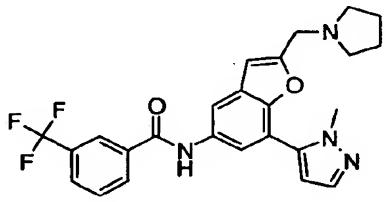
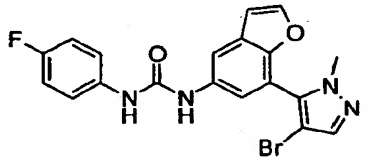
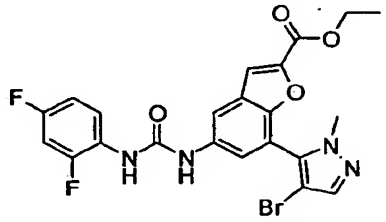
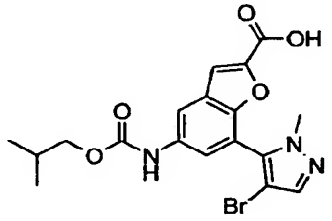
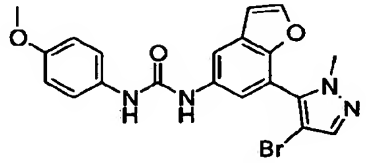
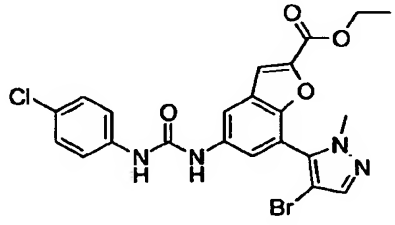
Example compounds of the present invention are provided below in Table 1. These compounds were found to be inverse agonists of the 5-HT_{2A} receptor according to one or more of the assays provided herein.

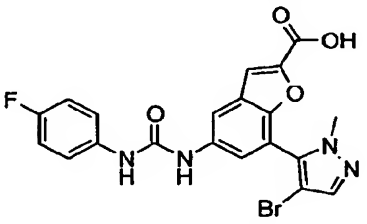
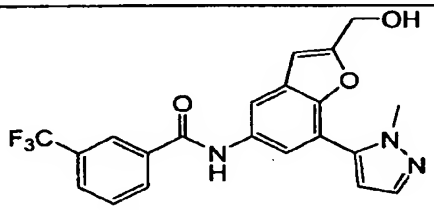
Table 1

Cmpd No.	Chemical Structure	Chemical Name
1		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-trifluoromethyl-phenyl)-urea
2		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid ethyl ester

Cmpd No.	Chemical Structure	Chemical Name
3		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-methoxy-phenyl)-urea
4		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid
5		N-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide
6		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(2,4-difluoro-phenyl)-urea
7		[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-carbamic acid 4-methoxy-phenyl ester
8		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-p-tolyl-urea
9		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester

Cmpd No.	Chemical Structure	Chemical Name
10		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-trifluoromethyl-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester
11		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea
12		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea
13		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-chloro-phenyl)-urea
14		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-isopropyl-phenyl)-urea
15		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid

Cmpd No.	Chemical Structure	Chemical Name
16		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester
17		N-[7-(2-Methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide
18		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-fluoro-phenyl)-urea
19		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester
20		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid
21		1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-methoxy-phenyl)-urea
22		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-chloro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester

Cmpd No.	Chemical Structure	Chemical Name
23		7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid
24		N-(2-(Hydroxymethyl)-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-5-yl)-3-(trifluoromethyl)benzamide

The compounds listed in Table 1 were prepared according to the methods described below. The compounds described herein, *supra* and *infra*, are named according to CS Chem Draw Ultra Version 7.0.1 or AutoNom 2000. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a 4 nucleus auto switchable probe and z-gradient or a Bruker Avance-400 or 500 MHz equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet, br = broad. Microwave irradiations were carried out using the Emrys Synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done *in vacuo* on a Buchi rotary evaporator. Celite 545® was used during palladium filtrations.

LCMS specs: 1) PC: HPLC-pumps: LC-10AD *VP*, Shimadzu Inc.; HPLC system controller: SCL-10A *VP*, Shimadzu Inc; UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2. 2) Mac: HPLC-pumps: LC-8A *VP*, Shimadzu Inc; HPLC system controller: SCL-10A *VP*, Shimadzu Inc.

UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex Software: Masschrom 1.5.2.

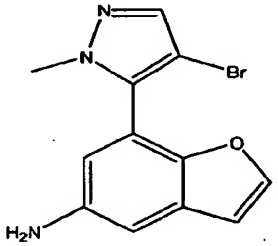
Example 1.1: Preparation of 1-Methyl-5-(5-nitrobenzofuran-7-yl)-1H-pyrazole (Intermediate).

To a suspension of 7-bromo-5-nitrobenzofuran (1.747 g, 7.22 mmol), 1-methyl-1H-pyrazol-5-ylboronic acid (1.788 g, 14.2 mmol), and Cs_2CO_3 (7.86 g, 24.1 mmol) in dimethoxy ethane (DME; 125 mL) under argon was added $Pd(PPh_3)_4$ (372 mg, 0.322 mmol). The reaction mixture was heated to 85 °C overnight, cooled to room temperature, and then diluted with water (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography to afford the title compound as a solid (708 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (d, J = 2.27 Hz, 1H), 8.28 (d, J = 2.27 Hz, 1H), 7.86 (d, J = 2.23 Hz, 1H), 7.64 (d, J = 1.94 Hz, 1H), 7.04 (d, J = 2.23 Hz, 1H), 6.60 (d, J = 1.95 Hz, 1H), 3.94 (s, 3H).

Example 1.2: Preparation of 4-Bromo-1-methyl-5-(5-nitrobenzofuran-7-yl)-1H-pyrazole (Intermediate).

To a solution of 1-methyl-5-(5-nitrobenzofuran-7-yl)-1H-pyrazole (680 mg, 2.80 mmol) in THF (25 mL) was added N-bromosuccinimide (NBS; 540 mg, 3.03 mmol) and stirred for one hour. The resulting material was purified by silica gel chromatography to afford the title compound as a solid (761 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, J = 2.27 Hz, 1H), 8.31 (d, J = 2.26 Hz, 1H), 7.85 (d, J = 2.24 Hz, 1H), 7.64 (s, 1H), 7.06 (d, J = 2.25 Hz, 1H), 3.83 (s, 3H).

Example 1.3: Preparation of 7-(4-Bromo-1-methyl-1H-pyrazol-5-yl)benzofuran-5-amine (Intermediate).



To a solution of 4-bromo-1-methyl-5-(5-nitrobenzofuran-7-yl)-1H-pyrazole (740 mg, 2.30 mmol) in ethanol (30 mL) and acetic acid (30 mL) was added iron powder (1.5 g, 27 mmol). The reaction mixture was heated to 75 °C for six hours, cooled to room temperature, filtered, and concentrated *in vacuo*. The resulting material was purified by HPLC to afford the title compound (349 mg, 52%). LCMS m/z (%) = 292 (M+H ^{79}Br, 98), 294 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.83 (d, J = 2.13 Hz, 1H), 7.69 (s, 1H), 6.90 (d, J = 2.20 Hz, 1H), 6.82 (d, J = 2.17 Hz, 1H), 6.62 (d, J = 2.18 Hz, 1H), 5.08 (bs, 2H), 3.69 (s, 3H).

Example 1.4: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea (Compound 12).

To a solution of 7-(4-bromo-1-methyl-1H-pyrazol-5-yl)benzofuran-5-amine (24.2 mg, 0.083 mmol) in CH_2Cl_2 (2 mL) was added 4-chlorophenyl isocyanate (15 mg, 0.098 mmol) and stirred overnight. The resulting white solid was collected by filtration to afford the title compound (15.7 mg, 43%). LCMS m/z (%) = 445 (M+H ^{79}Br, 72), 447 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.90 (bs, 1H), 8.89 (bs, 1H), 8.03 (d, J = 2 Hz, 1H), 7.95 (d, J = 2 Hz, 1H), 7.75 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 2 Hz, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 2 Hz, 1H), 3.73 (s, 3H).

Example 1.5: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(2,4-difluoro-phenyl)-urea (Compound 6).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 447 (M+H ^{79}Br, 100), 449 (M+H ^{81}Br, 87). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.20 (bs, 1H), 8.54 (bs, 1H), 8.12-8.04 (m, 1H), 8.03 (d, J = 2.16 Hz, 1H), 7.95 (d, J = 2.14 Hz, 1H), 7.75 (s, 1H), 7.39 (d, J = 2.11 Hz, 1H), 7.36-7.28 (m, 1H), 7.09-7.02 (m, 2H), 3.73 (s, 3H).

Example 1.6: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-methoxy-phenyl)-urea (Compound 21).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 441 (M+H ^{79}Br, 100), 443 (M+H ^{81}Br, 87). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77 (bs, 1H), 8.53 (bs, 1H), 8.02 (d, J = 2.15 Hz, 1H), 7.95 (d, J = 2.10 Hz, 1H), 7.75 (s, 1H), 7.42-7.34 (m, 3H), 7.04 (d, J = 2.19 Hz, 1H), 6.87 (d, J = 9.04 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H).

Example 1.7: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-fluoro-phenyl)-urea (Compound 18).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 429 (M+H ^{79}Br, 96), 431 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.85 (bs, 1H), 8.76 (bs, 1H), 8.02 (d, J = 2.16 Hz, 1H), 7.95 (d, J = 2.11 Hz, 1H), 7.75 (s, 1H), 7.51-7.44 (m, 2H), 7.39 (d, J = 2.10 Hz, 1H), 7.17-7.09 (m, 2H), 7.05 (d, J = 2.18 Hz, 1H), 3.73 (s, 3H).

Example 1.8: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-chloro-phenyl)-urea (Compound 13).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 445 (M+H ^{79}Br, 70), 447 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.96 (bs, 1H), 8.95 (bs, 1H), 8.03 (d, J = 2.16 Hz, 1H), 7.96 (d, J = 2.13 Hz, 1H), 7.75 (s, 1H), 7.75-7.71 (m, 1H), 7.40 (d, J = 2.11 Hz, 1H), 7.34-7.27 (m, 2H), 7.06 (d, J = 2.16 Hz, 1H), 7.04-6.99 (m, 1H), 3.73 (s, 3H).

Example 1.9: Preparation of [7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-carbamic acid 4-methoxy-phenyl ester (Compound 7).

To a solution of 7-(4-bromo-1-methyl-1H-pyrazol-5-yl)benzofuran-5-amine (21.2 mg, 0.073 mmol) and pyridine (30 μL) in CH_2Cl_2 (2 ml) was added 4-methoxyphenyl chloroformate (13 μL, 0.087 mmol) and stirred overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel chromatography to afford the title compound as a white solid (24.1 mg, 75%). LCMS m/z (%) = 442 (M+H ^{79}Br, 81), 444 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.93 (bs, 1H), 7.71 (d, J = 2.18 Hz, 1H), 7.57 (s, 1H), 7.35 (d, J = 2.19 Hz, 1H), 7.17 (bs, 1H), 7.12 (d, J = 9.06 Hz, 2H), 6.92 (d, J = 9.07 Hz, 2H), 6.89 (d, J = 2.21 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H).

Example 1.10: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-methoxy-phenyl)-urea (Compound 3).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 441 (M+H ^{79}Br, 100), 443 (M+H ^{81}Br, 91). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.84 (bs, 1H), 8.74 (bs, 1H), 8.02 (d, J = 2.16 Hz, 1H), 7.97 (d, J = 2.14 Hz, 1H), 7.75 (s, 1H), 7.38 (d, J = 2.11 Hz, 1H), 7.23-7.15 (m, 2H), 7.06 (d, J = 2.17 Hz, 1H), 6.97-6.92 (m, 1H), 6.58-6.53 (m, 1H), 3.73 (s, 6H).

Example 1.11: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-trifluoromethyl-phenyl)-urea (Compound 1).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 479 (M+H ^{79}Br, 94), 481 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.19 (bs, 1H), 9.02 (bs, 1H), 8.04 (d, J = 2.14 Hz, 1H), 7.98 (d, J = 2.12 Hz, 1H), 7.76 (s, 1H), 7.69 (d, J = 8.90 Hz, 2H), 7.64 (d, J = 8.97 Hz, 2H), 7.42 (d, J = 2.11 Hz, 1H), 7.07 (d, J = 2.15 Hz, 1H), 3.74 (s, 3H).

Example 1.12: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-isopropyl-phenyl)-urea (Compound 14).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 453 (M+H ^{79}Br, 100), 455 (M+H ^{81}Br, 95). ^{1}H NMR (400

MHz, DMSO-d_6) δ: 8.82 (bs, 1H), 8.63 (bs, 1H), 8.02 (d, J = 2.15 Hz, 1H), 7.96 (d, J = 2.09 Hz, 1H), 7.75 (s, 1H), 7.40-7.35 (m, 3H), 7.15 (d, J = 8.52 Hz, 2H), 7.05 (d, J = 2.18 Hz, 1H), 3.73 (s, 3H), 2.83 (septet, J = 6.91 Hz, 1H), 1.18 (d, J = 6.90 Hz, 6H).

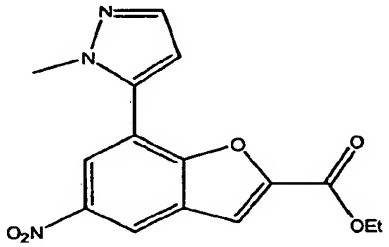
Example 1.13: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-p-tolyl-urea (Compound 8).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 425 (M+H ^{79}Br, 100), 427 (M+H ^{81}Br, 91). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.80 (bs, 1H), 8.60 (bs, 1H), 8.02 (d, J = 2.15 Hz, 1H), 7.95 (d, J = 2.11 Hz, 1H), 7.74 (s, 1H), 7.38 (d, J = 2.11 Hz, 1H), 7.34 (d, J = 8.42 Hz, 2H), 7.08 (d, J = 8.28 Hz, 2H), 7.05 (d, J = 2.19 Hz, 1H), 3.73 (s, 3H), 2.24 (s, 3H).

Example 1.14: Preparation of Ethyl 7-Bromo-5-nitrobenzofuran-2-carboxylate (Intermediate).

A solution of 7-bromo-5-nitrobenzofuran-2-carboxylic acid (3.38 g, 11.8 mmol) in 1.25M HCl in ethanol (150 mL) was heated to reflux for two hours. The reaction mixture was concentrated *in vacuo* to afford the title compound as a solid (3.413 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (d, J = 2.16 Hz, 1H), 8.55 (d, J = 2.15 Hz, 1H), 7.70 (s, 1H), 4.49 (q, J = 7.12 Hz, 2H), 1.45 (t, J = 7.15 Hz, 3H).

Example 1.15: Preparation of Ethyl 7-(1-Methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-carboxylate (Intermediate).



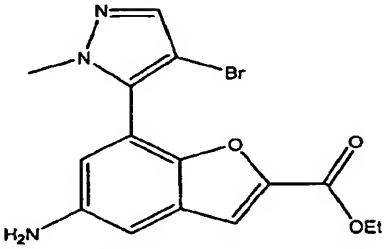
The title compound was prepared in a similar manner as described in Example 1.1 to give a solid. LCMS m/z (%) = 316 (M+H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (d, J = 2.27 Hz, 1H), 8.41 (d, J = 2.26 Hz, 1H), 7.72 (s, 1H), 7.68 (d, J = 2.00 Hz, 1H), 6.67 (d, J = 2.01 Hz, 1H), 4.46 (q, J = 7.13 Hz, 2H), 4.00 (s, 3H), 1.43 (t, J = 7.14 Hz, 3H).

Example 1.16: Preparation of Ethyl 7-(4-Bromo-1-methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-carboxylate (Intermediate).

The title compound was prepared in a similar manner as described in Example 1.2 to give a white solid. LCMS m/z (%) = 394 (M+H ^{79}Br, 95), 396 (M+H ^{81}Br, 100). ^{1}H NMR (400

MHz, $CDCl_3$) δ: 8.75 (d, J = 2.27 Hz, 1H), 8.46 (d, J = 2.27 Hz, 1H), 7.73 (s, 1H), 7.66 (s, 1H), 4.46 (q, J = 7.13 Hz, 2H), 3.87 (s, 3H), 1.43 (t, J = 7.12 Hz, 3H).

Example 1.17: Preparation of Ethyl 5-Amino-7-(4-bromo-1-methyl-1H-pyrazol-5-yl)benzofuran-2-carboxylate (Intermediate).



The title compound was prepared in a similar manner as described in Example 1.3 to give a yellow solid. LCMS m/z (%) = 364 (M+H ^{79}Br, 100), 366 (M+H ^{81}Br, 98). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.74 (s, 1H), 7.64 (s, 1H), 6.97 (d, J = 2.25 Hz, 1H), 6.84 (d, J = 2.26 Hz, 1H), 5.33 (bs, 2H), 4.32 (q, J = 7.10 Hz, 2H), 3.71 (s, 3H), 1.30 (t, J = 7.10 Hz, 3H).

Example 1.18: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-chloro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (Compound 22).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 517 (M+H ^{79}Br, 100), 519 (M+H ^{81}Br, 82). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.05 (bs, 1H), 8.94 (bs, 1H), 8.14 (d, J = 2.15 Hz, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.57 (d, J = 2.14 Hz, 1H), 7.51 (d, J = 8.92 Hz, 2H), 7.34 (d, J = 8.90 Hz, 2H), 4.35 (q, J = 7.10 Hz, 2H), 3.76 (s, 3H), 1.32 (t, J = 7.11 Hz, 3H).

Example 1.19: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (Compound 19).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 519 (M+H ^{79}Br, 89), 521 (M+H ^{81}Br, 100). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.32 (bs, 1H), 8.57 (bs, 1H), 8.14 (d, J = 1.95 Hz, 1H), 8.10-8.04 (m, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.55 (d, J = 2.27 Hz, 1H), 7.36-7.30 (m, 1H), 7.09-7.03 (m, 1H), 4.35 (q, J = 6.96 Hz, 2H), 3.76 (s, 3H), 1.32 (t, J = 7.04 Hz, 3H).

Example 1.20: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid (Compound 15).

To a solution of 7-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (23.8 mg, 0.0458 mmol) in methanol (1 mL) and THF (5 mL) was added 1M LiOH in water (1 mL). After one hour, the organic solvents were removed *in vacuo* and the remaining aqueous mixture acidified by the addition of 1M HCl.

The resulting white solid was collected by filtration to afford the title compound (17.8 mg, 79%). LCMS m/z (%) = 491 (M+H ^{79}Br, 100), 493 (M+H ^{81}Br, 86). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.70 (bs, 1H), 9.32 (bs, 1H), 8.58 (bs, 1H), 8.12 (d, J = 2.14 Hz, 1H), 8.11-8.04 (m, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.54 (d, J = 2.13 Hz, 1H), 7.38-7.29 (m, 1H), 7.10-7.03 (m, 1H), 3.76 (s, 3H).

Example 1.21: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (Compound 9).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 513 (M+H ^{79}Br, 92), 515 (M+H ^{81}Br, 100).

Example 1.22: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid (Compound 4).

The title compound was prepared in a similar manner as described in Example 1.20 to give a white solid. LCMS m/z (%) = 485 (M+H ^{79}Br, 100), 487 (M+H ^{81}Br, 95).

Example 1.23: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid ethyl ester (Compound 2).

The title compound was prepared in a similar manner as described in Example 1.9 to give a white solid. LCMS m/z (%) = 464 (M+H ^{79}Br, 78), 466 (M+H ^{81}Br, 100).

Example 1.24: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (Compound 16).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 501 (M+H ^{79}Br, 92), 503 (M+H ^{81}Br, 100).

Example 1.25: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-trifluoromethyl-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester (Compound 10).

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid. LCMS m/z (%) = 551 (M+H ^{79}Br, 100), 553 (M+H ^{81}Br, 89).

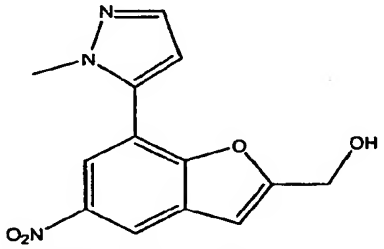
Example 1.26: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid (Compound 23).

The title compound was prepared in a similar manner as described in Example 1.20 to give a white solid. LCMS m/z (%) = 473 (M+H ^{79}Br, 88), 475 (M+H ^{81}Br, 100).

Example 1.27: Preparation of 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid (Compound 20).

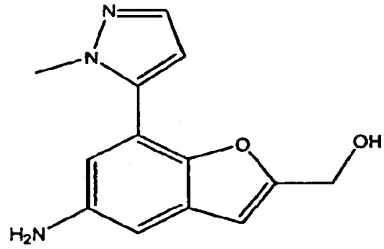
The title compound was prepared in a similar manner as described in Example 1.20 to give a white solid. LCMS m/z (%) = 436 (M+H ^{79}Br, 100), 438 (M+H ^{81}Br, 93).

Example 1.28: Preparation of (7-(1-Methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-yl)methanol (Intermediate).



To a solution of ethyl 7-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-carboxylate (804 mg, 2.55 mmol) in CH_2Cl_2 (30 mL) and THF (20 mL) was added 1M DIBAL-H in THF (30 mL, 30 mmol) and stirred for three hours. The reaction was quenched by addition of methanol (1 mL) and aqueous sodium potassium tartrate (150 mL). After stirring for two hours, the mix was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 250 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting material was purified by HPLC to afford the title compound as a yellow solid (282 mg, 40%). LCMS m/z (%) = 274 (M+H, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.69 (d, J = 2.34 Hz, 1H), 8.21 (d, J = 2.34 Hz, 1H), 7.62 (d, J = 1.92 Hz, 1H), 7.10 (s, 1H), 6.68 (d, J = 1.92 Hz, 1H), 5.67 (t, J = 6.00 Hz, 1H), 4.64 (d, J = 5.89 Hz, 2H), 3.85 (s, 3H).

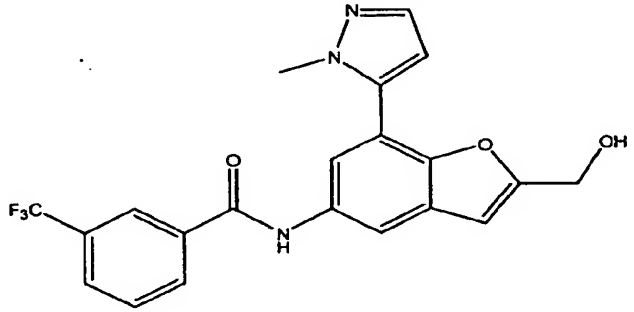
Example 1.29: Preparation of (5-Amino-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-2-yl)methanol (Intermediate).



To a solution of (7-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-yl)methanol (217 mg, 0.794 mmol) in methanol (20 mL) was added 5% Pd/C (56.3 mg). The reaction mixture was stirred under Hydrogen for three days and then filtered through celite (washing with 100 mL methanol). The mixture was concentrated *in vacuo* and purified by HPLC to afford the title compound as a tan solid (45 mg, 34%). LCMS m/z (%) = 244 (M+H, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51 (d, J = 1.85 Hz, 1H), 6.77 (d, J = 2.20 Hz, 1H), 6.61-6.58 (m, 2H),

6.42 (d, J = 1.85 Hz, 1H), 5.38 (t, J = 5.94 Hz, 1H), 4.97 (bs, 2H), 4.47 (d, J = 5.90 Hz, 2H), 3.77 (s, 3H).

Example 1.30: Preparation of N-(2-(Hydroxymethyl)-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-5-yl)-3-(trifluoromethyl)benzamide. (Compound 24)

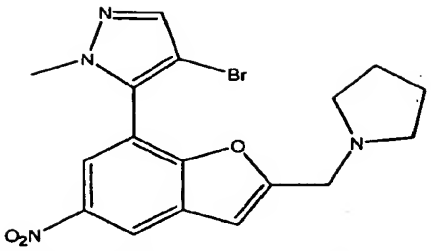


To a solution of (5-amino-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-2-yl)methanol (44 mg, 0.181 mmol) and triethylamine (70 µL) in CH_2Cl_2 (5 mL) was added 3-(trifluoromethyl)benzoyl chloride (27 µL, 0.179 mmol) and stirred for two hours. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by HPLC to afford the title compound as a white solid (49.8 mg, 66%). LCMS m/z (%) = 416 (M+H, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.60 (bs, 1H), 8.35-8.27 (m, 2H), 8.18 (d, J = 2.00 Hz, 1H), 8.02-7.96 (m, 1H), 7.85-7.77 (m, 1H), 7.69 (d, J = 2.05 Hz, 1H), 7.58 (d, J = 1.87 Hz, 1H), 6.91 (s, 1H), 6.55 (d, J = 1.89 Hz, 1H), 4.58 (bs, 2H), 3.84 (s, 3H).

Example 1.31: Preparation of N-[7-(2-Methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide (Compound 17).

To a solution of *N*-(2-(hydroxymethyl)-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-5-yl)-3-(trifluoromethyl)benzamide (49 mg, 0.118 mmol) and triethylamine (30 µL) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (15 µL, 0.194 mmol) and stirred overnight. Pyrrolidine (50 µL, 0.609 mmol) was added and stirring continued overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by HPLC to afford the title compound as a white solid (15.8 mg, 29%). LCMS m/z (%) = 469 (M+H, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.60 (bs, 1H), 8.34-8.27 (m, 2H), 8.16 (d, J = 2.00 Hz, 1H), 7.99 (d, J = 7.86 Hz, 1H), 7.81 (t, J = 7.78 Hz, 1H), 7.68 (d, J = 2.00 Hz, 1H), 7.59 (d, J = 1.87 Hz, 1H), 6.91 (s, 1H), 6.55 (d, J = 1.87 Hz, 1H), 3.84 (s, 3H), 3.77 (bs, 2H), 2.61-2.50 (m, 4H), 1.76-1.65 (m, 4H).

Example 1.32: Preparation of 4-Bromo-1-methyl-5-(5-nitro-2-(pyrrolidin-1-ylmethyl)benzofuran-7-yl)-1H-pyrazole (Intermediate).



To a solution of (7-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzofuran-2-yl)methanol (275 mg, 1.01 mmol) and triphenylphosphine (274.5 mg, 1.05 mmol) in dimethylacetamide (DMA; 30 mL) was added NBS (197.1 mg, 1.11 mmol). After two hours, LC/MS analysis showed that the reaction was not complete, so additional triphenylphosphine (254 mg, 0.97 mmol) was added, followed by NBS (282 mg, 1.58 mmol). Two hours later, more NBS (305 mg, 1.71 mmol) was added. An hour later, pyrrolidine (0.500 mL, 6.09 mmol) was added and the reaction mixture was heated to 145 °C for 20 min. The reaction mixture was purified by HPLC to afford the title compound as a brown solid (282 mg, 69%). LCMS m/z (%) = 405 (M+H ^{79}Br, 100), 407 (M+H ^{81}Br, 92). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (d, J = 2.33 Hz, 1H), 8.25 (d, J = 2.36 Hz, 1H), 7.81 (s, 1H), 7.13 (s, 1H), 3.83 (s, 2H), 3.77 (s, 3H), 2.58-2.45 (m which overlaps with DMSO, 4H), 1.71-1.64 (m, 4H).

Example 1.33: Preparation of 4-Bromo-1-methyl-5-(5-amino-2-(pyrrolidin-1-ylmethyl)benzofuran-7-yl)-1H-pyrazole (Intermediate).

To a stirred mixture of 4-bromo-1-methyl-5-(5-nitro-2-(pyrrolidin-1-ylmethyl)benzofuran-7-yl)-1H-pyrazole (200 mg, 0.494 mmol), saturated aqueous NH_4Cl solution (0.5 mL), and THF (10 mL) at 0 °C, was added zinc dust (280 mg, 4.28 mmol). After warming to room temperature overnight, the reaction mixture was filtered through celite and purified by HPLC to afford the title compound as a yellow wax (90.5 mg, 49%). LCMS m/z (%) = 375 (M+H ^{79}Br, 100), 377 (M+H ^{81}Br, 71). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.69 (s, 1H), 6.82 (d, J = 2.21 Hz, 1H), 6.62 (s, 1H), 6.55 (d, J = 2.20 Hz, 1H), 5.04 (bs, 2H), 3.69 (s, 3H), 3.66 (s, 2H), 2.52-2.45 (m which overlaps with DMSO, 4H), 1.71-1.65 (m, 4H).

Example 1.34: Preparation of 1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea (Compound 11).

To a solution of 4-bromo-1-methyl-5-(5-amino-2-(pyrrolidin-1-ylmethyl)benzofuran-7-yl)-1H-pyrazole (39 mg, 0.104 mmol) in CH_2Cl_2 (5 mL) was added 4-chlorophenyl isocyanate (20 mg, 0.130 mmol) and stirred overnight. The reaction mixture was purified by HPLC to afford the title compound as a white solid (49.4 mg, 90%). LCMS m/z (%) = 528 (M+H ^{79}Br, 66), 530 (M+H ^{81}Br, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.86 (bs, 1H), 8.85 (bs, 1H), 7.87 (d, J = 2.06 Hz, 1H), 7.74 (s, 1H), 7.50 (d, J = 8.88 Hz, 2H), 7.35-7.31 (m, 3H), 6.84 (s, 1H), 3.75-3.72 (m, 5H), 2.53-2.49 (m which overlaps with DMSO, 4H), 1.72-1.67 (m, 4H).

Example 1.35: Preparation of N-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide (Compound 5).

To a solution of 4-bromo-1-methyl-5-(5-amino-2-(pyrrolidin-1-ylmethyl)benzofuran-7-yl)-1H-pyrazole (39.4 mg, 0.105 mmol) and triethylamine (50 μL) in CH_2Cl_2 (5 mL) was added 3-(trifluoromethyl)benzoyl chloride (18 μL, 0.122 mmol) and stirred overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by HPLC to afford the title compound as a white solid (30.1 mg, 52%). LCMS m/z (%) = 547 (M+H ^{79}Br, 100), 549 (M+H ^{81}Br, 85). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.64 (bs, 1H), 8.35-8.22 (m, 3H), 7.99 (d, J = 7.77 Hz, 1H), 7.81 (t, J = 7.81 Hz, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 6.95 (bs, 1H), 3.83-3.72 (m, 5H), 2.61-2.49 (m which overlaps with DMSO, 4H), 1.77-1.67 (m, 4H).

Example A

Receptor Expression

A. pCMV

Although a variety of expression vectors are available to those in the art, it is preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

B. Transfection procedure

For the IP accumulation assay (hereinbelow), HEK293 cells were transfected. For the DOI binding assay (hereinbelow) COS7 cells were transfected. Several protocols well known in the art can be used to transfect cells. The following protocol is representative of the transfection procedures used herein for COS7 or 293 cells.

On day one, COS-7 cells were plated onto 24 well plates, usually 1x105 cells/well or 2x105 cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 ug cDNA in 50 μl serum-free DMEM/well and then 2 μL lipofectamine in 50 μL serum-free DMEM/well. The solutions ("transfection media") were gently mixed and incubated for 15-30 minutes at room temperature. The cells were washed with 0.5 mL PBS and then 400 μL of serum free media was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37 °C / 5% CO_2. Then the transfection media was removed and replaced with 1 mL/well of regular growth media.

For 293 cells, on day one, 13x106 293 cells per 150 mm plate were plated out. On day two, 2 mL of serum OptimemI (Invitrogen Corporation) was added per plate followed by addition of 60 μL of lipofectamine and 16 μg of cDNA. Note that lipofectamine must be added to the OptimemI and mixed well before addition of cDNA. While complexes between lipofectamine and the cDNA are forming, media was carefully aspirated and cells were gently rinsed with 5 mL of OptimemI media followed by careful aspiration. Then 12 mL of OptimemI was added to each plate and 2 mL of transfection solution was added followed by a 5 hour incubation at 37 °C in a 5% CO_2 incubator. Plates were then carefully aspirated and 25 mL of Complete Media were added to each plate and cells were then incubated until used.

Example B

Inositol Phosphate (IP) Accumulation Assays

A. 5-HT_{2A} receptor

Compounds of the invention can be tested for their ability to activate a 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, HEK293 cells are transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, sequence no. 24) as described in Example A. An IP accumulation assay can be performed as described below.

B. Constitutively active 5-HT_{2A} receptor

Compounds of the invention were tested for their ability to inhibit a constitutively active 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, 293 cells were transiently transfected with a pCMV expression vector containing a constitutively active human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, sequence no. 30) as described in Example A. The constitutively active human 5-HT_{2A} receptor contained the human 5-HT_{2A} receptor described in part A except that intracellular loop 3 (IC3) and the cytoplamic tail were replaced by the corresponding human INI 5-HT_{2C} cDNA. An IP accumulation assay was performed as described below. Certain compounds of the invention had activity values ranging from about 10 μM to about 0.8 nM in this assay.

C. IP Accumulation Assay protocol

On the day after transfections, media is removed and the cells are washed with 5 mL PBS followed by careful aspiration. Cells are then trypsinized with 2 mL of 0.05% trypsin for 20-30 seconds followed by addition of 10 mL of warmed media, gently titurated to dissociate cells, and an additional 13 mL of warmed media is gently added. Cells are then counted and 55,000 cells are added to 96-well sterile poly-D-lysine treated plates. Cells are allowed to attach over a six hour incubation at 37 °C in a 5% CO_2 incubator. Media is then carefully aspirated and

100 μL of warm inositol-free media plus 0.5 μCi 3H-inositol is added to each well and the plates are incubated for 18-20 hours at 37 °C in a 5% CO_2 incubator.

On the next day, media is carefully aspirated and then 0.1 mL of assay medium is added containing inositol-free/serum free media, 10 μM pargyline, 10 mM lithium chloride, and test compound at indicated concentrations. The plates are then incubated for three hours at 37 °C and then wells are carefully aspirated. Then 200 μL of ice-cold 0.1M formic acid is added to each well. Plates can then be frozen at this point at –80 °C until further processing. Frozen plates are then thawed over the course of one hour, and the contents of the wells (approximately 220 μL) are placed over 400 μL of washed ion-exchange resin (AG 1-X8) contained in a Multi Screen Filtration plate and incubated for 10 minutes followed by filtration under vacuum pressure. Resin is then washed nine times with 200 μL of water and then tritiated inositol phosphates (IP, IP2, and IP3) are eluted into a collecting plate by the addition of 200 μL of 1M ammonium formate and an additonal 10 minute incubation. The elutant is then transferred to 20 mL scintillation vials, 8 mL of SuperMix or Hi-Safe scintillation cocktails is added, and vials are counted for 0.5-1 minutes in a Wallac 1414 scintilation counter.

Example C

Binding Assays

Compounds of the invention were tested for their ability to bind to a 5-HT_{2A} receptor clone membrane preparation using a radioligand binding assay. Briefly, COS cells were transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, sequence no. 24) as described in Example A.

A. Preparation of Crude Membrane Preparations for Radioligand Binding Assays

COS7 cells transfected with recombinant human 5-HT_{2A} receptors were cultured for 48 hr post transfection, collected, washed with ice-cold phosphate buffered saline, pH7.4 (PBS), and then centrifuged at 48,000Xg for 20 min at 4 °C. The cell pellet was then resuspended in wash buffer containing 20 mM HEPES pH 7.4 and 0.1 mM EDTA, homogenized on ice using a Brinkman polytron, and recentrifuged at 48,000 X g for 20 min. at 4 °C. The resultant pellet was then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice, and centrifuged (48,000Xg for 20 min at 4 °C). Crude membrane pellets were stored at –80 °C until used for radioligand binding assays.

B. [^{125}I]DOI Radioligand Binding Assay

Radioligand binding assays for human 5-HT_{2A} receptor was conducted using the 5-HT_2 agonist [^{125}I]DOI as radioligand. To define nonspecific binding, 10 μM DOI was used for all

assays. For competitive binding studies, 0.5 nM [^{125}I]DOI was used and compounds were assayed over a range of 0.01 nM to 10 μM. Assays were conducted in a total volume of 200 μL in 96-well Perkin Elmer GF/C filter plates in assay buffer (50 mM Tris-HCl, pH 7.4, 0.5 mM EDTA, 5 mM $MgCl_2$, and 10 μM pargyline). Assay incubations were performed for 60 min at room temperature and were terminated by rapid filtration under vacuum pressure of the reaction mixture over Whatman GF/C glass fiber filters presoaked in 0.5% PEI using a Brandell cell harvestor. Filters were then washing several times with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4). Plates were then dried at room temperature and counted in a Wallac microBeta scintillation counter. Certain other compounds of the invention had activity values ranging from about 10 μM to about 0.2 nM in this assay.

Example D

In Vitro Human Platelet Aggregation Assays

Compounds of the invention can be tested for their ability to aggregate human platelets. Aggregation assays are performed using a Chrono-Log Optical aggregometer model 410. Human blood (~100 mL) is collected from human donors into glass Vacutainers containing 3.8% sodium citrate (light blue tops) at room temperature. Platelet rich plasma (PRP) is isolated via centrifugation at 100 g for 15 min at room temperature. After removal of the aqueous PRP layer, the platelet poor plasma (PPP) is prepared via high speed centrifugation at 2400 g for 20 min. Platelets are counted and their concentration is set to 250,000 cells/μL by dilution with PPP. Aggregation assays are conducted according to the manufacturer's specifications. Briefly, a suspension of 450 μL PRP is stirred in a glass cuvette (1200 rpm) and, after baseline was established, 1 μM ADP followed by either saline or 1 μM 5HT and compound of interest (at desired concentrations) are added and the aggregation response recorded. The concentration of ADP used causes approximately 10-20% of maximal aggregation. The 5-HT concentration corresponds to the concentration which produced maximal potentiation. Percent inhibition of aggregation is calculated from the maximum decrease in optical density of the controls and of the samples containing inhibitors.

Example E

Efficacy of Compounds of the Invention in the Attenuation of DOI-induced hypolocomotion in rats

In this example, compounds of the invention can be tested for inverse agonist activity by determining whether these compounds could attenuate DOI-induced hypolocomotion in rats in a novel environment. DOI is a potent 5-$HT_{2A/2C}$ receptor agonist that crosses the blood-brain barrier. The standard protocol used is described briefly below.

Animals:

Male Sprague-Dawley rats weighing between 200-300g are used for all tests. Rats are housed three to four per cage. These rats are naïve to experimental testing and drug treatment. Rats are handled one to three days before testing to acclimate them to experimental manipulation. Rats are fasted overnight prior to testing.

Compounds:

(R)-DOI HCl ($C_{11}H_{16}INO_2 \cdot HCl$) can be obtained from Sigma-Aldrich, and is dissolved in 0.9% saline. Compounds of the invention are synthesized at Arena Pharmaceuticals Inc. and are dissolved in 100% PEG400. DOI is injected s.c. in a volume of 1 mL/kg, while compounds of the invention are administered p.o. in a volume of 2mL/kg.

Procedure:

The "Motor Monitor" (Hamilton-Kinder, Poway, CA) is used for all activity measurement. This apparatus recorded rears using infrared photobeams.

Locomotor activity testing is conducted during the light cycle (0630-1830) between 9:00 a.m. and 4:00 p.m. Animals are allowed 30 min acclimation to the testing room before testing began.

In determining the effects of compounds of the invention on DOI-induced hypoactivity, animals are first injected with vehicle or the compound of the invention (50 μmol/kg) in their home cages. Sixty minutes later, saline or DOI (0.3 mg/kg salt) is injected. 10 min after DOI administration, animals are placed into the activity apparatus and rearing activity is measured for 10 minutes.

Statistics and Results:

Results (total rears over 10 minutes) are analyzed by t-test. $P<0.05$ is considered significant.

Example F

In vitro Binding of 5-HT_{2A} Receptor

Animals:

Animals (Sprague-Dawley rats) are sacrificed and brains are rapidly dissected and frozen in isopentane maintained at -42 °C. Horizontal sections are prepared on a cryostat and maintained at -20 °C.

LSD Displacement Protocol:

Lysergic acid diethylamide (LSD) is a potent 5-HT_{2A} receptor and dopamine D2 receptor ligand. An indication of the selectivity of compounds for either or both of these receptors involves displacement of radiolabeled-bound LSD from pre-treated brain sections. For these studies, radiolabeled ^{125}I-LSD (NEN Life Sciences, Boston, Mass., Catalogue number NEX-199) can be utilized; spiperone (RBI, Natick, Mass. Catalogue number s-128) a 5-HT_{2A} receptor and dopamine D2 receptor antagonist, can also utilized. Buffer consists of 50 nanomolar TRIS-HCl, pH 7.4.

Brain sections are incubated in (a) Buffer plus 1 nanomolar ^{125}I-LSD; (b) Buffer plus 1 nanomolar ^{125}I-LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar ^{125}I-LSD and 1 micromolar compound of interest for 30 minutes at room temperature. Sections are then washed 2 x 10 minutes at 4 °C in Buffer, followed by 20 seconds in distilled H_2O. Slides are then air-dried.

After drying, sections are apposed to X-ray film (Kodak Hyperfilm) and exposed for 4 days.

Example G

Serotonin 5-HT_{2A} Receptor Occupancy Studies in Monkey

In this example, the 5-HT_{2A} receptor occupancy of a compound of the invention can be measured. The study can be carried out in rhesus monkeys using PET and 18F-altanserin.

Radioligand:

The PET radioligand used for the occupancy studies is ^{18}F-altanserin. Radiosynthesis of ^{18}F-altanserin is achieved in high specific activities and is suitable for radiolabeling 5-HT_{2A} receptors in vivo (see Staley et al., Nucl. Med. Biol., 28:271-279 (2001) and references cited within). Quality control issues (chemical and radiochemical purity, specific activity, stability etc) and appropriate binding of the radioligand are verified in rat brain slices prior to use in PET experiments.

Drug Doses and Formulations:

Briefly, the radiopharmaceutical is dissolved in sterile 0.9% saline, pH approx 6-7. The compounds of the invention are dissolved in 60% PEG 400 - 40% sterile saline on the same day of the PET experiment.

Serotonin 5-HT_{2A} occupancy studies in humans have been reported for M100,907 (Grunder et al., Neuropsychopharmacology, 17:175-185 (1997), and Talvik-Lofti et al., Psychopharmacology, 148:400-403 (2000)). High occupancies of the 5-HT_{2A} receptors have been reported for various oral doses (doses studied ranged from 6 to 20 mg). For example, an occupancy of >90% was reported for a dose of 20 mg (Talvik-Lofti et al., supra), which

translates to approx. 0.28 mg/kg. It may therefore be anticipated that an i.v. dose of 0.1 to 0.2 mg/kg of M100,907 is likely to provide high receptor occupancy. A 0.5 mg/kg dose of a Compound of the invention can be used in these studies.

PET Experiments:

The monkey is anesthetized by using ketamine (10 mg/kg) and is maintained using 0.7 to 1.25% isoflurane. Typically, the monkey has two i.v. lines, one on each arm. One i.v. line is used to administer the radioligand, while the other line is used to draw blood samples for pharmacokinetic data of the radioligand as well as the cold drugs. Generally, rapid blood samples are taken as the radioligand is administered which then taper out by the end of the scan. A volume of approximately 1 mL of blood is taken per time point, which is spun down, and a portion of the plasma is counted for radioactivity in the blood.

An initial control study is carried out in order to measure baseline receptor densities. PET scans on the monkey are separated by at least two weeks. Unlabeled Compound of the invention is administered intravenously, dissolved in 80% PEG 400:40% sterile saline.

PET Data Analysis:

PET data are analyzed by using cerebellum as the reference region and using the distribution volume region (DVR) method. This method has been applied for the analysis of 18F-altanserin PET data in nonhuman primate and human studies (Smith et al., Synapse, 30:380-392 (1998).

Example H

The Effect of Compounds of the Invention and Zolpidem on Delta Power in Rats

In this example, the effect of compounds of the invention on sleep and wakefullness can be compared to the reference drug zolpidem. Drugs are administered during the middle of the light period (inactivity period).

Briefly, compounds of the invention are tested for their effects on sleep parameters and are compared to zolpidem (5.0 mg/kg, Sigma, St. Louis, MO) and vehicle control (80% Tween 80, Sigma, St. Louis, MO). A repeated measures design is employed in which each rat is to receive seven separate dosings via oral gavage. The first and seventh dosings are vehicle and the second through sixth are the test compounds and zolpidem given in counter-balanced order. Since all dosings are administered while the rats are connected to the recording apparatus, 60% CO_2/40% O_2 gas is employed for light sedation during the oral gavage process. Rats are fully recovered within 60 seconds following the procedure. A minimum of three days elapses between dosings. In order to test the effect of the compounds on sleep consolidation, dosing occurs during the middle of the rats' normal inactive period (6 hours following lights on). Dosing typically occurs between 13:15 and 13:45 using a 24 hour notation. All dosing solutions

are made fresh on the day of dosing. Following each dosing, animals are continuously recorded until lights out the following day (~30 hours).

Animal Recording and Surgical Procedures:

Animals are housed in a temperature controlled recording room under a 12/12 light/dark cycle (lights on at 7:00 am) and have food and water available ad libitum. Room temperature (24+2 °C), humidity (50+20% relative humidity) and lighting conditions are monitored continuously via computer. Drugs are administered via oral gavage as described above, with a minimum of three days between dosings. Animals are inspected daily in accordance with NIH guidelines.

Eight male Wistar rats (300 + 25 g; Charles River, Wilmington, MA) are prepared with chronic recording implants for continuous electroencephalograph (EEG) and electromyograph (EMG) recordings. Under isoflurane anesthesia (1-4%), the fur is shaved from the top of the skull and the skin was disinfected with Betadine and alcohol. A dorsal midline incision is made, the temporalis muscle retracted, and the skull cauterized and thoroughly cleaned with a 2% hydrogen peroxide solution. Stainless steel screws (#000) are implanted into the skull and served as epidural electrodes. EEG electrodes are positioned bilaterally at +2.0 mm AP from bregma and 2.0 mm ML and at -6.0 mm AP and 3.0 mm ML. Multi-stranded twisted stainless steel wire electrodes are sutured bilaterally in the neck muscles for recording of the EMG. EMG and EEG electrodes are soldered to a head plug connector that was affixed to the skull with dental acrylic. Incisions are closed with suture (silk 4-0) and antibiotics administered topically. Pain is relieved by a long-lasting analgesic (Buprenorphine) administered intramuscularly once post-operatively. Post-surgery, each animal is placed in a clean cage and observed until it is recovered. Animals are permitted a minimum of one week post-operative recovery before study.

For sleep recordings, animals are connected via a cable and a counter-balanced commutator to a Neurodata model 15 data collection system (Grass-Telefactor, West Warwick, RI). The animals are allowed an acclimation period of at least 48 hours before the start of the experiment and are connected to the recording apparatus continuously throughout the experimental period except to replace damaged cables. The amplified EEG and EMG signals are digitized and stored on a computer using SleepSign software (Kissei Comtec, Irvine CA).

Data Analysis:

EEG and EMG data are scored visually in 10 second epochs for waking (W), REMS, NREMS. Scored data are analyzed and expressed as time spent in each state per half hour. Sleep bout length and number of bouts for each state are calculated in hourly bins. A "bout" consists of a minimum of two consecutive epochs of a given state. EEG delta power (0.5-3.5

Hz) within NREMS is also analyzed in hourly bins. The EEG spectra during NREMS are obtained offline with a fast Fourier transform algorithm on all epochs without artifact. The delta power is normalized to the average delta power in NREMS between 23:00 and 1:00, a time when delta power is normally lowest.

Data are analyzed using repeated measures ANOVA. Light phase and dark phase data are analyzed separately. Both the treatment effect within each rat and the time by treatment effect within each rat is analyzed. Since two comparisons are made, a minimum value of $P<0.025$ is required for post hoc analysis. When statistical significance is found from the ANOVAs, t-tests are performed comparing all compounds to vehicle and the test compounds to zolpidem.

Example I

Efficacy of Compounds of the Invention in the Inhibition of JC Virus Infection of Human Glial Cells

A compound of the invention can be shown to inhibit JC virus infection of human glial cells using the in vitro model of Elphick et al. [Science (2004) 306:1380-1383], essentially as described briefly here.

Cells and JC Virus

The human glial cell line SVG (or a suitable subclone thereof, such as SVG-A) is used for these experiments. SVG is a human glial cell line established by transformation of human fetal glial cells by an origin defective SV40 mutant [Major et al., Proc. Natl. Acad. Sci. USA (1985) 82:1257-1261]. SVG cells are cultured in Eagle's minimum essential medium (Mediatech Inc., Herndon, VA) supplemented with 10% heat-inactivated fetal bovine serum, and kept in a humidified 37°C 5% CO2 incubator.

The Mad-1/SVEΔ strain of JC virus [Vacante et al., Virology (1989) 170:353-361] is used for these experiments. While the host range of JC virus is typically limited to growth in human fetal glial cells, the host range of Mad-1/SVEΔ extends to human kidney and monkey cell types. Mad-1/SVEΔ is propagated in HEK cells. Virus titer is measured by hemagglutination of human type O erythrocytes.

Assay for Inhibition of JC Virus Infection

SVG cells growing on coverslips are pre-incubated at 37 °C for 45 min with or without the compound of the invention diluted in media containing 2% FCS. By way of illustration and not limitation, the compound of the invention is used at a concentration of about 1 nM to about 100 μM, at a concentration of about 10 nM to about 100 μM, at a concentration of about 1 nM to about 10 μM, or at a concentration of about 10 nM to about 10 μM.

JC virus (Mad-1/SVEΔ) is then added at an MOI of 1.0 and the cells are incubated for 1 hr at 37 °C in the continued presence of the compound of the invention. The cells are then washed 3X in PBS and fed with growth media containing the compound of the invention. At 72 hr post-infection, V antigen positive cells are scored by indirect immunofluorescence (see below). Controls include the addition of the compound of the invention at 24 and 48 h post-infection. The percentage of infected cells in untreated cultures is set at 100%.

Indirect Immunofluorescence

For indirect immunofluorescence analysis of V antigen expression, SVG cells growing on coverslips are fixed in ice cold acetone. To detect V antigen expression, the cells are then incubated for 30 min at 37 °C with a 1:10 dilution of hybridoma supernatant from PAB597. The PAB597 hybridoma produces a monoclonal antibody against the SV40 capsid protein VP1 which has been shown to cross-react with JC virus VP1. The cells are then washed and incubated with goat anti-mouse Alexa Fluor 488 secondary antibody for an additional 30 min. After a final wash, the cells are counterstained with 0.05% Evan's blue, mounted onto glass slides using 90% glycerol in PBS and visualized on Nikon E800 epifluorescent scope. Images are captured using a Hamamatsu digital camera and analyzed using Improvision software.

Example J

In Vitro Dog Platelet Aggregation Assays

Approximately 50 mL of blood is pooled from 3 male beagles. The protocol for analyzing the effects of compounds on platelet aggregation are identical to those used for human platelets (see Example D, supra) except 5 μM ADP and 2 μM 5-HT are used to stimulate amplification of platelet aggregation.

Example K

Ex-Vivo Dog Whole Blood Aggregation

One hour following PO dosing with a test compound whole blood is collected from male beagle dogs in a 5 mL vacutainer with exogenous heparin (5 U/mL) added to vacutainer. Aggregation studies are evaluated by using whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 μL) is added to saline (600 μL) with constant stirring and activated with 5 μg of Collagen (Chronolog Corp.). The serotonin response is obtained by adding 5-HT (Sigma) to final concentration of 2.5 μM. Results: Selected compounds are tested for anti-platelet aggregation activity after single bolus oral dosing. The dose that affords maximal inhibition of 5-HT amplified platelet aggregation is identified and used for comparison.

Example L

Rat In Vivo Thrombosis, Bleeding, Aggregation, PK Assay

Thrombosis formation and Bleeding time:

This model concomitantly measures thrombus formation, bleeding time, platelet aggregation and drug exposure in a single live dosed rat. Test compounds are administered to male rats (weighing 250-350 g) via PO injection at varying concentrations depending on compound potency ranging from 1 mpk-100 mpk. Animals are then anesthetized using Nembutal approximately 30 min post PO. Once the animal is fully anesthetized using approved surgical techniques the animal's right femoral artery is isolated in 2 different sections approximately 4-6 mm in length, one area for probe placement and one for Ferric Chloride patch positioning. The artery is then allowed to stabilize to allow recovery from the surgery. During stabilization the animal is then intubated and placed on a ventilator (Harvard Apparatus, Inc.) at 75 strokes/min with a volume of 2.5 cubic cm. Following intubation and after stabilization a micro arterial probe (Transonic Systems, Inc) is then placed on the distal isolated femoral artery. Once the probe is in place the flow is monitored using a Powerlab recording system (AD Instruments) to monitor rate of pulsatile flow. A small piece of filter paper soaked in 30% ferric chloride is placed on the area of the artery upstream of the probe for 10 min. After 5 min of Ferric Choloride patch placement the last 3 mm of the rat's tail is removed. The tail is then placed in a saline filled glass vial at 37 degree and the time it takes for bleeding to stop is recorded. After the Ferric chloride patch is removed the flow was recorded until the artery is occluded and time to occlusion is recorded.

Whole Blood Aggregation and PK:

Following measurement of bleeding and time to occlusion 5 mL of blood is obtained for ex-vivo aggregation analysis by cardiac puncture in heparin (5U/mL). An additional 500 µL of blood is collected in a separate vacutainer for PK analysis (plasma drug concentration). Ex-vivo aggregation studies are evaluated by using whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 µL) is added to saline (600 µL) with constant stirring and activated with 2.55 µg of Collagen (Chronolog Corp.). The serotonin response is obtained by adding 5-HT (Sigma) to final concentration of 2.5 µM. Results: Test compounds or reference compounds with acceptable levels of binding to rat 5-HT_{2A} receptors are evaluated for effects of thrombus formation, bleeding and platelet activity in a single model. This allows for the most accurate demonstration of separation of the test compound effects on platelet mediated thrombus formation from effects on bleeding.

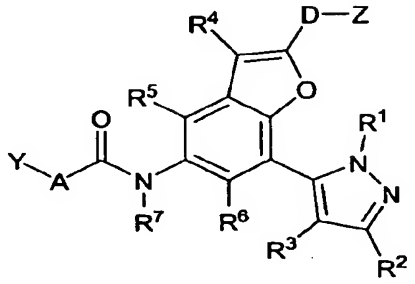
Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but are not limited to, printed

publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety.

Claims

What is claimed is:

1. A compound selected from compounds of Formula I and pharmaceutically acceptable salts, solvates and hydrates thereof:



I

wherein:

A is absent, O or NR^8;

D is absent, C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, O, S, NR^9, CO, COO, $CONR^9$, SO, SO_2, $SONR^9$, or NR^9CONR^{10};

Y is C_{1-10} alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$;

Z is H, C_{1-10} alkyl, NR'R", aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is H or C_{1-6} alkyl;

R^2 and R^3 are independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}C(O)OR^{a2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^4, R^5, and R^6 are independently selected from H, halo, and C_{1-4} alkyl;

R^7, R^8, R^9, and R^{10} are independently selected from H and C_{1-4} alkyl;

Cy is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$;

R' and R" are independently selected from H, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a, R^{a1}, and R^{a2} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^b, R^{b1}, and R^{b2} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^c and R^d are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^{c1} and R^{d1} are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

R^{c2} and R^{d2} are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; and

R^e, R^{e1}, and R^{e2} are independently selected from H, CN, and NO_2.

2. The compound according to claim 1, wherein A is absent.

3. The compound according to claim 1, wherein A is O.

4. The compound according to claim 1, wherein A is NR^8.

5. The compound according to claim 1, wherein A is NH.

6. The compound according to any one of claims 1 to 5, wherein Y is C_{1-10} alkyl, aryl, or heteroaryl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$,

$C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

7. The compound according to any one of claims 1 to 5, wherein Y is C_{1-10} alkyl or aryl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

8. The compound according to any one of claims 1 to 5, wherein Y is C_{1-10} alkyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

9. The compound according to any one of claims 1 to 5, wherein Y is C_{1-10} alkyl.

10. The compound according to any one of claims 1 to 5, wherein Y is isobutyl.

11. The compound according to any one of claims 1 to 5, wherein Y is phenyl optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from Cy, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

12. The compound according to any one of claims 1 to 5, wherein Y is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^a.

13. The compound according to any one of claims 1 to 12, wherein D is absent, C_{1-4} alkylene, or COO.

14. The compound according to any one of claims 1 to 12, wherein D is absent.

15. The compound according to any one of claims 1 to 12, wherein D is C_{1-4} alkylene.

16. The compound according to any one of claims 1 to 12, wherein D is COO.

17. The compound according to any one of claims 1 to 16, wherein Z is H, C_{1-10} alkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

18. The compound according to any one of claims 1 to 16, wherein Z is H, C_{1-10} alkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

19. The compound according to any one of claims 1 to 16, wherein Z is H, C_{1-10} alkyl, or heterocycloalkyl.

20. The compound according to any one of claims 1 to 19, wherein –D-Z is, H, C(O)O-(C_{1-10} alkyl), COOH, or heterocycloalkyl-(C_{1-10}) alkyl.

21. The compound according to any one of claims 1 to 20, wherein R^1 is H or methyl.

22. The compound according to any one of claims 1 to 20, wherein R^1 is methyl.

23. The compound according to any one of claims 1 to 22, wherein R^2 and R^3 are independently selected from H and halo.

24. The compound according to any one of claims 1 to 23, wherein R^2 is H.

25. The compound according to any one of claims 1 to 23, wherein R^3 is H or halo.

26. The compound according to any one of claims 1 to 23, wherein R^3 is H.

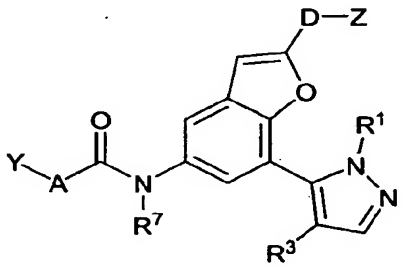
27. The compound according to any one of claims 1 to 23, wherein R^3 is halo.

28. The compound according to any one of claims 1 to 23, wherein R^3 is Br.

29. The compound according to any one of claims 1 to 28, wherein R^4, R^5, and R^6 are each H.

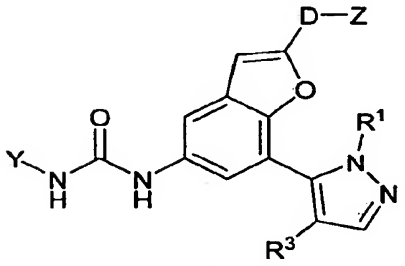
30. The compound according to any one of claims 1 to 29, wherein R^7 is H.

31. The compound of claim 1 having Formula II:

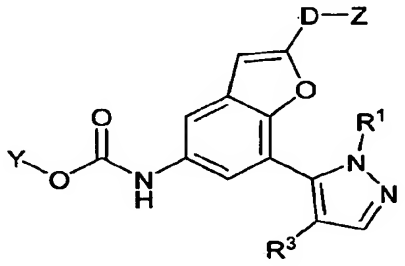


II

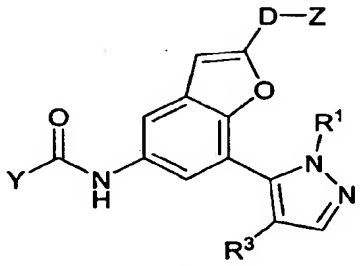
32. The compound of claim 1 having Formula IIIa, IIIb, or IIIc:



IIIa



IIIb



IIIc

33. The compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates or hydrates thereof:

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-trifluoromethyl-phenyl)-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid ethyl ester;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-methoxy-phenyl)-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid;

N-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(2,4-difluoro-phenyl)-urea

[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-carbamic acid 4-methoxy-phenyl ester;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-p-tolyl-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-methoxy-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-trifluoromethyl-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-chloro-phenyl)-urea;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(3-chloro-phenyl)-urea;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-isopropyl-phenyl)-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester;

N-[7-(2-Methyl-2H-pyrazol-3-yl)-2-pyrrolidin-1-ylmethyl-benzofuran-5-yl]-3-trifluoromethyl-benzamide;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-fluoro-phenyl)-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(2,4-difluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-isobutoxycarbonylamino-benzofuran-2-carboxylic acid;

1-[7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-benzofuran-5-yl]-3-(4-methoxy-phenyl)-urea;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-chloro-phenyl)-ureido]-benzofuran-2-carboxylic acid ethyl ester;

7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-[3-(4-fluoro-phenyl)-ureido]-benzofuran-2-carboxylic acid; and

N-(2-(Hydroxymethyl)-7-(1-methyl-1H-pyrazol-5-yl)benzofuran-5-yl)-3-(trifluoromethyl)benzamide.

34. A composition comprising a compound according to any one of claims 1 to 33 and at least one pharmaceutically acceptable carrier.

35. A method for treating a 5-HT_{2A} related disorder in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

36. The method according to claim 35, wherein said 5-HT_{2A} related disorder is selected from coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

37. A method for treating a condition associated with platelet aggregation in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

38. A method for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery in a patient, comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

39. A method for reducing the risk of blood clot formation in a patient suffering from atrial fibrillation, comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

40. A method for treating a sleep disorder in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

41. The method according to claim 40, wherein said sleep disorder is a dyssomnia.

42. The method according to claim 40, wherein said sleep disorder is insomnia.

43. The method according to claim 40, wherein said sleep disorder is a parasomnia.

44. A method for treating a diabetic-related disorder in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

45. A method for treating progressive multifocal leukoencephalopathy in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

46. A method for treating hypertension in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

47. A method for treating pain in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 33.

48. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in the treatment of a 5-HT_{2A} related disorder.

49. The use of claim 48 wherein said 5-HT_{2A} related disorder is selected from coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

50. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in the treatment of a condition associated with platelet aggregation.

51. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in reducing the risk of blood clot formation in a patient undergoing an angioplasty or coronary bypass surgery.

52. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in reducing the risk of blood clot formation in a patient.

53. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in reducing the risk of blood clot formation in a patient suffering from atrial fibrillation.

54. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating a sleep disorder.

55. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating a dyssomnia.

56. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating insomnia.

57. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating a parasomnia.

58. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating a diabetic-related disorder.

59. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating progressive multifocal leukoencephalopathy.

60. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating hypertension.

61. Use of a compound according to any one of claims 1 to 33 in the production of a medicament for use in treating pain.

62. A compound according to any one of claims 1 to 33 for use in a method of treatment of the human or animal body by therapy.

63. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a 5-HT_{2A} related disorder in the human or animal body by therapy.

64. The compound according to claim 63, wherein said 5-HT_{2A} related disorder is selected from coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

65. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a condition associated with platelet aggregation.

66. A compound according to any one of claims 1 to 33 for use in a method of reducing the risk of blood clot formation in a patient undergoing an angioplasty or coronary bypass surgery.

67. A compound according to any one of claims 1 to 33 for use in a method of reducing the risk of blood clot formation in a patient.

68. A compound according to any one of claims 1 to 33 for use in a method of reducing the risk of blood clot formation in a patient suffering from atrial fibrillation.

69. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a sleep disorder in the human or animal body by therapy.

70. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a dyssomnia.

71. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a insomnia.

72. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a parasomnia.

73. A compound according to any one of claims 1 to 33 for use in a method for the treatment of a diabetic-related disorder in the human or animal body by therapy.

74. A compound according to any one of claims 1 to 33 for use in a method for the treatment of progressive multifocal leukoencephalopathy in the human or animal body by therapy.

75. A compound according to any one of claims 1 to 33 for use in a method for the treatment of hypertension.

76. A compound according to any one of claims 1 to 33 for use in a method for the treatment of pain.

77. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 33 and at least one pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/04 A61K31/4155 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/055734 A (ARENA PHARM INC [US]; TEEGARDEN BRADLEY [US]; XIONG YIFENG [US]; STRAH) 26 May 2006 (2006-05-26) the whole document	1-77
Y	WO 2005/012254 A (ARENA PHARM INC [US]; TEEGARDEN BRADLEY [US]; JAYAKUMAR HONNAPPA [US];) 10 February 2005 (2005-02-10) the whole document	1-77

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2008	05/02/2008

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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